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(54) Title: GABA B RECEPTOR

(57) Abstract

The present invention features a novel $GABA_B$ receptor subtype ("$GABA_BR2$"). The cDNA sequence encoding $GABA_BR2$ is shown in Figures (1a–1n) as SEQ. ID. NO: 1. The $GABA_BR2$ amino acid sequence is provided in Figures (2a–2f) as SEQ. ID NO: 4.

GABA$_B$ RECEPTOR

RELATED APPLICATIONS

The present application claims priority to Garrett *et al.* U.S. Serial No. 60/080,676, filed April 3, 1998, which is hereby incorporated by reference herein in its entirety including the drawings.

FIELD OF THE INVENTION

The present invention relates to a GABA$_B$ receptor, nucleic acid encoding a GABA$_B$ receptor, and uses of a GABA$_B$ receptor and nucleic acid encoding a GABA$_B$ receptor.

BACKGROUND

The references cited herein are not admitted to be prior art to the claimed invention.

GABA$_B$ receptors are metabotropic receptors coupled to guanine-nucleotide-binding proteins (G-proteins). GABA$_B$ receptors modulate synaptic transmission by inhibiting presynaptic transmitter release and by increasing K^+ conductance responsible for long-lasting inhibitory postsynaptic potentials. (Kaupmann *et al., Nature 386*:239-246, 1997, hereby incorporated by reference herein.)

GABA$_B$ receptors are found in the mammalian brain, in locations outside of the brain, and in lower species. Outside of the brain, GABA$_B$ receptors have been identified on axon terminals and ganglion cell bodies of the autonomic nervous system, on fallopian tube and uterine intestinal smooth muscle cells, in the kidney cortex, urinary bladder muscle and on testicular interstitial cells. (*See,* Bowery, *Annu. Rev. Pharmacol. Toxicol. 33*:109-147, 1993, hereby incorporated by reference herein.)

GABA$_B$ receptors have been targeted to achieve therapeutic effects. Kerr and Ong, DDT 1:371-380, 1996, describe different compounds indicated to be GABA$_B$ receptor agonists and GABA$_B$ receptor antagonists. Kerr and Ong also review therapeutic implications of affecting GABA receptor activity including,

spasticity and motor control, analgesia, epilepsy, cognitive effects, psychiatric disorders, alcohol dependence and withdrawal, feeding behavior, cardiovascular and respiratory functions, and peripheral functions.

Bittiger *et al., Tips 4*:391-394, 1993, review therapeutic applications of $GABA_B$ receptor antagonists. Potential therapeutic applications noted by Bittiger *et al.* include cognitive processes, epilepsy, and depression.

Kaupmann *et al., Nature 386*:239-246, 1997, indicate that they cloned $GABA_B$ receptors. Two $GABA_B$ receptor proteins were indicated to be cloned from rat brain: $GABA_BR1a$ and $GABA_BR1b$. $GABA_BR1a$ differs from $GABA_BR1b$ in that the N-terminal 147 residues are replaced by 18 amino acids. $GABA_BR1a$ and $GABA_BR1b$ appear to be splice variants. The cloned $GABA_B$ receptors were indicated to negatively couple to adenylyl cyclases and show sequence similarity to the metabotropic receptors for L-glutamate(mGluR).

Kaupmann *et al., Nature 386*:239-246, 1997, indicate that bestfit sequence alignments with $GABA_B$ and different mGluR subtypes indicates 18-23% amino acid sequence identity and 43-48% related residues. (Devereux *et al., Nucleic Acids Res. 12*:387-395, 1984, was referenced for carrying out bestfit sequence alignments.) No significant sequence similarity was found with $GABA_A$ or $GABA_C$ receptors, or with other G-protein-coupled receptors which were not mGluR.

Kaupmann *et al.,* International Application Number PCT/EP97/01370, International Publication Number WO 97/46675, indicate that they have obtained rat $GABA_B$ clones, $GABA_BR1a$ and $GABA_BR1b$; and human $GABA_B$ clones, $GABA_BR1a/b$ (representing a partial receptor clone) and $GABA_BR1b$ (representing a full-length receptor clone). Amino acid sequence information, and encoding cDNA sequence information, is provided for the different human $GABA_B$ clones.

SUMMARY OF THE INVENTION

The present invention features a novel $GABA_B$ receptor subtype ("$GABA_BR2$"). The cDNA sequence encoding $GABA_BR2$ is shown in Figures 1a-1n as SEQ. ID. NO. 1. The $GABA_BR2$ amino acid sequence is provided in Figures 2a-2f as SEQ. ID. NO. 4.

Thus, a first aspect of the present invention describes a purified nucleic acid containing at least 18 contiguous nucleotides of SEQ. ID. NO. 1 which provides the nucleic acid encoding $GABA_BR2$. Preferably, the nucleic acid contains at least 27 contiguous nucleic acids, more preferably at least 45 contiguous nucleic acids, or most preferably the entire nucleic acid sequence provided in SEQ. ID. NO. 1. Advantages of longer-length nucleic acid include producing longer-length protein fragments having the sequence of $GABA_BR2$ which can be used, for example, to produce antibodies; and increased nucleic acid probe specificity under higher stringent hybridization assay conditions.

By "purified" in reference to nucleic acid is meant the nucleic acid is present in a form (*i.e.*, its association with other molecules) other than found in nature. For example, a purified receptor nucleic acid is separated from one or more nucleic acids which are present on the same chromosome. Preferably, the purified nucleic acid has been separated from at least 90% of the other nucleic acids present on the same chromosome. More preferably, the nucleic acid has been substantially purified such that it represents at least 75%, more preferably at least 85%, and most preferably at least 95% of the total nucleic acids present.

Another example of purified nucleic acid is recombinant nucleic acid. Preferably, recombinant nucleic acid contains nucleic acid encoding $GABA_BR2$ or $GABA_BR2$ fragments cloned in a vector. The vector contains the necessary elements for introducing heterologous nucleic acid into cells for either expression or replication.

Preferably, the vector is an expression vector containing elements needed for expressing a cloned nucleic acid sequence to produce a polypeptide. The expression vector contains a promoter region directing the initiation of RNA transcription, and DNA sequences which when transcribed into RNA signal protein synthesis initiation.

Recombinant nucleic acid may contain nucleic acid encoding for $GABA_BR2$, a $GABA_BR2$ fragment, or a $GABA_BR2$ derivative, under the control of genomic $GABA_BR2$ nucleic acid regulatory elements, or under the control of exogenous regulatory elements including

an exogenous promoter. By "exogenous" is meant a promoter that is not normally coupled *in vivo* transcriptionally to the coding sequence for $GABA_BR2$.

Another aspect of the present invention features a purified nucleic acid encoding at least 6 contiguous amino acids of the $GABA_BR2$ amino acid sequence which is provided as SEQ. ID. NO. 4. Due to the degeneracy of the genetic code, different combinations of nucleotides encode for the same polypeptide. Thus, numerous $GABA_BR2$ and $GABA_BR2$ fragments having the same amino acid sequences can be encoded for by different nucleic acid sequences. In preferred embodiments, the nucleic acid encodes at least 12, at least 18, at least 54 contiguous amino acids, or the entire amino acid sequence provided in SEQ. ID. NO. 4.

Another aspect of the present invention features a recombinant cell. The recombinant cell, which can be a tissue cell, is made up of a recombinant nucleic acid encoding $GABA_BR2$, a functional $GABA_BR2$ derivative, or a fragment thereof, and a cell able to express the nucleic acid. Recombinant cells have various uses including acting as biological factories to produce large amounts of polypeptides encoded for by the recombinant nucleic acid, as tools for screening for compounds which modulate $GABA_BR$ activity, and as research tools to study the effects of $GABA_BR$ activity.

Another aspect of the present invention features a purified nucleic acid comprising a nucleic acid sequence region substantially complementary to a sequence region of the SEQ. ID. NO. 1 or the perfect complement of SEQ. ID. NO. 1. Such nucleic acid can be used, for example, to specifically detect the presence of nucleic acid encoding for $GABA_BR2$ or a close relative thereof.

Substantially complementary nucleic acid regions contain at least 18 nucleotides in a stretch of 20 contiguous nucleotides which are complementary. Complementary nucleic acid form Watson-Crick A-T, G-C, and A-U, hydrogen bonds. More preferably, the nucleic acid comprises a nucleotide sequence of 20 contiguous nucleotides which has at least 19 bases, most preferably 20 bases, complementary to the nucleic acid sequence provided in SEQ. ID. NO. 1 or the perfect complement of SEQ. ID. NO. 1.

Another aspect of the present invention features a purified

polypeptide having at least 6 contiguous amino acids of the $GABA_BR2$ amino acid sequence. By "purified" in reference to a polypeptide is meant that the polypeptide is in a form (*i.e.*, its association with other molecules) distinct from naturally occurring polypeptides. Preferably, the polypeptide has been substantially purified to represent at least 75%, more preferably 85%, most preferably 95% of the total protein present in a preparation. In preferred embodiments, the purified polypeptide has at least 12 contiguous, at least 18 contiguous, at least 54 contiguous, or the entire amino acid sequence of SEQ. ID. NO. 4.

Another aspect of the present invention features a $GABA_BR2$-binding agent comprising a molecule which binds to a polypeptide consisting of the amino acid sequence of SEQ. ID. NO. 4. The binding agent is preferably a purified antibody. Other examples of binding agents include organic compounds which bind to $GABA_BR2$.

By "purified" in reference to a binding agent, such as an antibody, is meant that the binding agent is in a form (*i.e.*, its association with other molecules) distinct from a naturally occurring binding agent, if the binding agent is found in nature. Preferably, the binding agent is an antibody provided as a purified preparation representing at least 1%, more preferably at least 50%, more preferably at least 85%, most preferably at least 95% of the total protein in the preparation.

Another aspect of the present invention describes a method of making a $GABA_BR2$ or a fragment thereof. The method is carried out by incubating recombinant cells containing nucleic acid encoding $GABA_BR2$ or a fragment thereof under conditions where the nucleic acid is expressed.

Another aspect of the present invention describes a method of selecting for compounds able to modulate $GABA_BR$ activity. The method comprises the steps of (a) contacting a recombinant cell functionally expressing $GABA_BR2$ with a first test compound; and (b) measuring the ability of said test compound to affect $GABA_BR$ activity. Compounds modulating $GABA_BR$ activity either evoke a $GABA_BR$ activity, potentiate $GABA_BR$ activity, or inhibit a $GABA_BR$ activity. Cells functionally expressing $GABA_BR2$ also express $GABA_BR1a$ and/or $GABA_BR1b$.

Preferably, the ability of a plurality of different test compounds to affect $GABA_BR$ activity are tested. In preferred

embodiments at least 5, at least 10, at least 50 different compounds, and at least 100 different compounds are tested over a span of one week.

Other aspects of the present invention describe coexpression systems and the use of such systems to measure the activity at, or screen compounds active at, $GABA_BR1a$, $GABA_BR1b$, or $GABA_BR2$, preferably $GABA_BR2$. The coexpression systems comprise at least one of $GABA_BR1a$ and $GABA_BR1b$, $GABA_BR2$, and Gqo5.

Other aspects of the present invention describe coexpression systems and the use of such systems to measure the activity at, or screen compounds active at, $GABA_BR1a$, $GABA_BR1b$, or $GABA_BR2$. The coexpression systems comprise at least one of $GABA_BR1a$ or $GABA_BR1b$, coexpressed with $GABA_BR2$ and Gqo5. The presence of Gqo5 provides for signal transduction swapping allowing for receptor activity to be measured by mobilization of intracellular calcium mediated by the activation of phospholipase C.

Assays using the coexpression systems described above can be used to screen chemical libraries for compounds that modulate $GABA_B$ receptors. For example, in different embodiments, a library of compounds containing 10 or more compounds is screened at once; and 10 or more compounds are individually tested over the course of eight hours.

Preferably, the coexpression system is present in an isolated cell. An "isolated cell" includes tissue cells and refers to a cell present in a different environment (including a different concentration), than it is normally found in nature.

In other aspects, the invention describes transgenic nonhuman mammals containing a transgene encoding $GABA_BR2$, a $GABA_BR2$ fragment, or a derivative thereof; or a gene affecting the expression of $GABA_BR2$; and methods of creating a transgenic nonhuman mammal containing a transgene encoding an $GABA_BR2$, a $GABA_BR2$ fragment, or a derivative thereof.

Various examples are described herein. These examples are not intended in any way to limit the claimed invention.

Other features and advantages of the invention will be apparent from the following drawing, the description of the invention, the examples, and the claims.

BRIEF DESCRIPTION OF DRAWINGS

Figures 1a-1n illustrate the nucleic acid sequences encoding for the human $GABA_BR2$ designated SEQ. ID. NO. 1, human $GABA_BR1a$ designated SEQ. ID. NO. 2, and human $GABA_BR1b$ designated SEQ. ID. NO. 3.

Figures 2a-2f illustrate the amino acid sequences of the human $GABA_BR2$ (SEQ. ID. NO. 4); the rat $GABA_bR1a$ (SEQ. ID. NO. 5); the rat $GABA_bR1b$ protein (SEQ. ID. NO. 6); the human $GABA_bR1a$ (SEQ. ID. NO. 7); and the human $GABA_bR1a$ (SEQ. ID. NO. 8).

Figures 3a-3d provides the human calcium receptor nucleic acid sequence and the encoded for amino acid sequence.

Figure 4 illustrates functional expression of $GABA_BR2$ in *Xenopus* oocytes.

DETAILED DESCRIPTION OF THE INVENTION

The present invention features $GABA_BR2$. $GABA_BR2$ is closely related to $GABA_BR1a$ and $GABA_BR1b$. Nucleic acid encoding for human $GABA_BR2$ has a sequence similarity of about 50% with nucleic acid encoding rat $GABA_BR1a$ and rat $GABA_BR1b$. Human $GABA_BR2$ has a sequence identity of about 40% with rat $GABA_BR1a$ and $GABA_BR1b$ amino acid sequence.

Nucleic acid encoding $GABA_BR2$ was cloned by first identifying a human nucleic acid sequence approximately 38% identical to the nucleic acid sequence of rat $GABA_BR1$. Exact match polymerase chain reaction (PCR) primers were designed based on sequences from the identified sequence and used to amplify human $GABA_BR2$ nucleic acid from a human cerebral cortex cDNA library. A PCR product encoding human $GABA_BR2$ was isolated and cloned.

Northern blot analysis revealed that an approximately 6.3 Kb human $GABA_BR2$ transcript was abundantly expressed in the human brain. Expression was not detected in the heart, placenta, lung, liver, skeletal muscle, kidney or pancreas under conditions where $GABA_BR2$ transcript was identified in the human brain. Within the human brain $GABA_BR2$ is broadly expressed at variable levels.

Compounds modulating $GABA_BR$ activity can be obtained, for example, by screening a group, or library, of compounds to identify those compounds having the desired activity and then synthesizing such compounds. Thus, included in the present

invention is a method of making a $GABA_BR$ active compound by first screening for a compound having desired properties and then chemically synthesizing that compound.

Nucleic Acid Encoding $GABA_BR2$

Nucleic acids encoding $GABA_BR2$ have a variety of different uses including one or more of the following: (1) producing receptor proteins which can be used, for example, for structure determination, to assay a molecule's activity on a receptor, and to obtain $GABA_BR2$ modulatory agents; (2) being sequenced to determine a receptor's nucleotide sequence which can be used, for example, as a basis for comparison with other receptors to determine conserved regions, determine unique nucleotide sequences for normal and altered receptors, and to determine nucleotide sequences to be used as target sites for antisense nucleic acids, ribozymes, hybridization detection probes, or PCR amplification primers; (3) as hybridization detection probes to detect the presence of a native receptor and/or a related receptor in a sample; (4) as PCR primers to generate particular nucleic acid sequence regions, for example, to generate regions to be probed by hybridization detection probes; and (5) to provide an extracellular domain, transmembrane domain, or extracellular domain for use in the construction of a chimeric receptor.

Hybridization probes and primers based on the $GABA_BR2$ sequence information provided herein can be used, for example, to obtain nucleic acid from different sources or to identify the presence of $GABA_BR2$ nucleic acid in a sample. Nucleic acid encoding proteins related to human $GABA_BR2$ can be obtained from human and nonhuman sources. Such related nucleic acids are useful for identifying important $GABA_BR2$ structural motifs and may also provide new therapeutic target sites.

Primer hybridization specificity to target nucleic acid can be adjusted by varying the hybridization conditions. When annealing at higher stringency conditions of 50-60°C, sequences which are greater than about 75% complementarity to the primer will be amplified. By employing lower stringency conditions, annealing at 35-37°C, sequences which are greater than about 40-50% complementarity to the primer will be amplified.

Hybridization assay probes can be designed to detect the presence of a particular nucleic acid target sequence perfectly complementary to the probe and target sequences of lesser complementarity by varying the hybridization conditions and probe design. Factors affecting probe design, such as length, G and C content, possible self-complementarity, and wash conditions, are well known in the art. (See, for example, Sambrook *et al.*, *Molecular Cloning,* Cold Spring Harbor Laboratory Press (1989).) Sambrook *et al.*, *Molecular Cloning,* also discusses the design and use of degenerative probes based on polypeptide sequence information.

Preferably, the nucleic acid probes targeted to $GABA_BR2$ nucleic acid distinguish $GABA_BR2$ nucleic acid from $GABA_B1a$ and $GABA_B1b$ nucleic acid. Such probes are readily designed by comparing the nucleic acid sequences of target $GABA_BR2$, and non-target $GABA_B1a$ and $GABA_B1b$, to obtain probes having proper probe:target and probe:non-target T_m characteristics. Preferably, the probe:target duplex T_m is at least about 5°C greater than the probe:non-target T_m.

Probes specific for a target contain a target complementary region and may also contain target non-complementary regions. The target non-complementary regions, if present, are designed not to affect the specificity of the probe. An example of a target non-complementary region is a nucleic acid sequence used as a capture sequence in a sandwich assay, where the capture sequence does not hybridize to target or non-target nucleic acids. (See, Stabinsky, U.S. Patent No. 4,739,044, and Ranki *et al.*, U.S. Patent No. 4,563,419, both of which are incorporated by reference herein.)

The probes can be used under conditions of proper stringency conditions where target and non-target nucleic acid are distinguished. As the stringency conditions are increased, the complementarity of two nucleic acids required to form a stable duplex is also increased.

As a general guideline, high stringency conditions (*e.g.*, hybridization at 50-65°C, 5X SSPC, 50% formamide, wash at 50-65°C, 0.5X SSPC) can be used to obtain hybridization between nucleic acid sequences having regions which are greater than about 90% complementary. Low stringency conditions (*e.g.*, hybridization at

35-37°C, 5X SSPC, 40-45% formamide, wash at 42°C 1X SSPC) can be used so that sequences having regions greater than 35-45% complementarity will hybridize to the probe.

If desired, nucleic acid probes may be labeled with a detectable label using techniques well known in the art. Examples of detectable labels include radiolabels, enzymes, fluorescent molecules, and chemiluminescent molecules.

Any tissue can be used as a source for genomic DNA. However, with respect to RNA, the most preferred source is tissues which express elevated levels of $GABA_BR2$ or related proteins.

Specific nucleic acids can also be produced enzymatically using a host transformed with a plasmid encoding for the desired nucleic acid. Additionally, standard techniques for chemically synthesizing nucleic acids include solid phase phosphoramidite chemical synthesis.

$GABA_BR2$ polypeptides

$GABA_BR2$ polypeptides made up of $GABA_BR2$, $GABA_BR2$ fragments, and derivatives thereof have different uses including, being used to produce antibodies to determine the presence of the protein, and being used to screen for compounds able to bind to the protein. $GABA_BR2$ polypeptides are preferably produced using recombinant nucleic acid techniques.

Polypeptides can also be synthesized using solid phase techniques. Solid-phase synthesis is commenced from the carboxy-terminal end of the peptide using an α-amino protected amino acid. BOC protective groups can be used for all amino groups even though other protective groups are suitable. For example, BOC-lys-OH can be esterified to chloromethylated polystyrene resin supports. The polystyrene resin support is preferably a copolymer of styrene with about 0.5 to 2% divinylbenzene as a cross-linking agent which causes the polystyrene polymer to be completely insoluble in certain organic solvents. *See* Stewart *et al.*, Solid-Phase Peptide Synthesis (1969), W.H. Freeman Co., San Francisco; and Merrifield, *J. Am. Chem. Soc.* *85*:2149-2154, 1963. These and other methods of peptide synthesis are also exemplified by U.S. Patent Nos. 3,862,925; 3,842,067; 3,972,859; and 4,105,602.

$GABA_BR2$ derivatives, and nucleic acid encoding for $GABA_BR2$ derivatives can be produced using techniques well known in the art based upon the present disclosure. $GABA_BR2$ derivatives have a sequence similarity of at least 70%, more preferably at least 90%, even more preferably at least 95% sequence similarity to the amino acid sequence provided in SEQ. ID. NO. 4. Sequence similarity is preferably determined using BLASTN (Altschul *et al., J. Mol. Biol. 215:*403-410, 1990.)

Examples of specific types of derivatives include amino acid alterations such as deletions, substitutions, additions, and amino acid modifications. A "deletion" refers to the absence of one or more amino acid residue(s) in the related polypeptide. An "addition" refers to the presence of one or more amino acid residue(s) in the related polypeptide. Additions and deletions to a polypeptide may be at the amino terminus, the carboxy terminus, and/or internal. Amino acid "modification" refers to the alteration of a naturally occurring amino acid to produce a non-naturally occurring amino acid. A "substitution" refers to the replacement of one or more amino acid residue(s) by another amino acid residue(s) in the polypeptide. Derivatives can contain different combinations of alterations including more than one alteration and different types of alterations.

While the effect of an amino acid change varies depending upon factors such as phosphorylation, glycosylation, intra-chain linkages, tertiary structure, and the role of the amino acid in the active site or a possible allosteric site, it is generally preferred that the substituted amino acid is from the same group as the amino acid being replaced. To some extent the following groups contain amino acids which are interchangeable: the basic amino acids lysine, arginine, and histidine; the acidic amino acids aspartic and glutamic acids; the neutral polar amino acids serine, threonine, cysteine, glutamine, asparagine and, to a lesser extent, methionine; the nonpolar aliphatic amino acids glycine, alanine, valine, isoleucine, and leucine (however, because of size, glycine and alanine are more closely related and valine, isoleucine and leucine are more closely related); and the aromatic amino acids phenylalanine, tryptophan, and tyrosine. In addition, although classified in different categories, alanine, glycine, and serine seem to be interchangeable to some extent,

and cysteine additionally fits into this group, or may be classified with the polar neutral amino acids.

While proline is a nonpolar neutral amino acid, its replacement represents difficulties because of its effects on conformation. Thus, substitutions by or for proline are not preferred, except when the same or similar conformational results can be obtained. The conformation conferring properties of proline residues may be obtained if one or more of these is substituted by hydroxyproline (Hyp).

Examples of modified amino acids include the following: altered neutral nonpolar amino acids such as ω-amino acids of the formula $H_2N(CH_2)_nCOOH$ where n is 2-6, sarcosine (Sar), t-butylalanine (t-BuAla), t-butylglycine (t-BuGly), N-methyl isoleucine (N-MeIle), and norleucine (Nleu); altered neutral aromatic amino acids such as phenylglycine; altered polar, but neutral amino acids such as citrulline (Cit) and methionine sulfoxide (MSO); altered neutral and nonpolar amino acids such as cyclohexyl alanine (Cha); altered acidic amino acids such as cysteic acid (Cya); and altered basic amino acids such as ornithine (Orn).

Preferred derivatives have one or more amino acid alteration(s) which do not significantly affect the receptor activity of the related receptor protein. In regions of the $GABA_BR2$ not necessary for receptor activity amino acids may be deleted, added or substituted with less risk of affecting activity. In regions required for receptor activity, amino acid alterations are less preferred as there is a greater risk of affecting receptor activity. Such alterations should be conservative alterations. For example, one or more amino acid residues within the sequence can be substituted by another amino acid of a similar polarity which acts as a functional equivalent.

Conserved regions tend to be more important for protein activity than non-conserved regions. Standard procedures can be used to determine the conserved and non-conserved regions important of receptor activity using *in vitro* mutagenesis techniques or deletion analyses and measuring receptor activity as described by the present disclosure.

Derivatives can be produced using standard chemical techniques and recombinant nucleic acid techniques.

Modifications to a specific polypeptide may be deliberate, as through site-directed mutagenesis and amino acid substitution during solid-phase synthesis, or may be accidental such as through mutations in hosts which produce the polypeptide. Polypeptides including derivatives can be obtained using standard techniques such as those described by Sambrook *et al.*, *Molecular Cloning*, Cold Spring Harbor Laboratory Press (1989). For example, Chapter 15 of Sambrook describes procedures for site-directed mutagenesis of cloned DNA.

$GABA_BR2$ Antibodies

Antibodies binding $GABA_BR2$ have various uses such as being used as therapeutic agents to modulate $GABA_BR$ activity; as diagnostic tools for determining $GABA_BR2$ number; as research tools for studying receptor synthesis, structure, and function; and as a tool by purifying $GABA_BR2$.

$GABA_BR2$, and $GABA_BR2$ fragments retaining antigenic determinants, can be used to generate antibodies recognizing $GABA_BR2$. Preferably, polypeptide fragments used to generate antibodies are at least six amino acid in length. Both polyclonal and monoclonal antibodies can be generated.

Antibodies can be produced using standard techniques such as those described by Harlow and Lane in *Antibodies, a Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. Sources of immunogens for antibody production include purified $GABA_BR2$, $GABA_BR2$ fragments, and whole cells expressing $GABA_BR2$. The present invention also includes hybridoma cells secreting monoclonal antibodies to $GABA_BR2$.

Recombinant Cells

Nucleic acid expressing a functional $GABA_BR2$ can be used to create transfected cells lines functionally expressing $GABA_BR2$. Such cell lines have a variety of uses such as being used for high-throughput screening for compounds modulating $GABA_BR$ activity; being used to assay binding to $GABA_BR2$; and as factories to produce large amounts of $GABA_BR2$, or $GABA_BR2$ fragments.

A variety of cell lines can couple exogenously expressed receptors to endogenous functional responses. Cell lines such as NIH-3T3, HeLa, NG115, CHO, HEK 293 and COS7 which are expected to

lack $GABA_BR2$ can be tested to confirm that they lack an endogenous $GABA_BR2$.

Production of stable transfectants can be accomplished by transfection of an appropriate cell line with an expression vector, such as the eukaryotic pMSG vectors. Expression vectors containing a promoter region, such as the mouse mammary tumor virus promoter (MMTV), drive high-level transcription of cDNAs in a variety of mammalian cells. In addition, these vectors contain genes for selecting cells stably expressing cDNA of interest. The selectable marker in the pMSG vectors encodes an enzyme, xanthine-guanine phosphoribosyl transferase (XGPRT), conferring resistance to a metabolic inhibitor that is added to the culture to kill nontransfected cells.

The most effective method for transfection of eukaryotic cell lines with plasmid DNA varies with the given cell type. The $GABA_BR2$ expression construct will be introduced into cultured cells by the appropriate technique, such as Ca^{2+} phosphate precipitation, DEAE-dextran transfection, lipofection or electroporation. Expression of the $GABA_BR2$ cDNA in cell lines can be assessed by solution hybridization and Northern blot analysis.

Assaying For Compounds Modulating $GABA_BR$ Activity

The ability of compounds to modulate $GABA_BR$ activity can be assayed by measuring alterations of cellular processes affected by $GABA_BR$ activity. Generally, a $GABA_BR2$ agonist is present when measuring antagonist activity. However, protein fusions can be created, for example, where an agonist extracellular binding domain of $GABA_BR2$ is swapped with the agonist binding domain of a different receptor allowing for the measurement of antagonist activity using an agonist of the different receptor; or where the intracellular domain of $GABA_BR2$ is swapped with the intracellular domain of a different receptor allowing for the measuring of $GABA_BR$ activity by measuring intracellular effects caused by the different receptor.

Chimeric proteins are preferably produced using recombinant nucleic acid techniques to provide an appropriate nucleic acid encoding for the chimeric protein. Preferably, portions of $GABA_BR2$ are swapped with portions of the calcium receptor. The $GABA_BR2$ extracellular domain is made up of approximately amino

acids 1-422 Of SEQ. ID. NO. 4, the $GABA_BR2$ transmembrane domain is made up of approximately amino acids 423-686 Of SEQ. ID. NO. 4, and the $GABA_BR2$ intracellular domain is made up of approximately amino acids 687-883 Of SEQ. ID. NO. 4. The human calcium receptor amino acid and encoding nucleic acid is provided in Figure 3. The calcium receptor extracellular domain is made up of approximately amino acids 1-612, the calcium receptor transmembrane domain is made up of approximately amino acids 613-862, and the calcium receptor intracellular domain is made up of approximately amino acids 863-1078. Calcium receptor activity can be measured using techniques well known in the art such as those described by Brown *et al.*, U.S. Patent No. 5,688,938, hereby incorporated by reference herein.

Binding Assays

The present invention also includes using $GABA_BR2$ and fragments thereof in binding assays. Binding assays can be carried out using techniques well known in the art. Binding assays preferably employ radiolabeled binding agents.

An example of a binding assay is carried out by first attaching $GABA_BR2$, or a fragment thereof, to a solid-phase support to create an affinity matrix. The affinity matrix is then contacted with potential $GABA_BR2$ binding agents. A large library of compounds may be used to determine those compounds binding to the affinity matrix. Bound compounds can be eluted from the column.

Transgenic Animals

The present invention also concerns the construction and use of transgenic animals, and transformed cells, encoding $GABA_BR2$. Transgenic nonhuman mammals are particularly useful as an *in vivo* test system for studying the effects of introducing $GABA_BR2$; regulating the expression of $GABA_BR2$ (*e.g.*, through the introduction of additional genes, antisense nucleic acids, or ribozymes); and studying the effect of compounds which mimic or block the effect of $GABA_BR2$.

Experimental model systems for studying the physiological role of the $GABA_BR2$ can be created having varying degrees of

receptor expression. For example, nucleic acid encoding a receptor may be inserted into cells naturally expressing the receptor such that the gene is expressed at much higher levels. Alternatively, a recombinant gene may be used to inactivate the endogenous gene by homologous recombination and, thereby, create an $GABA_BR2$ deficient cell, tissue, or animal.

Inactivation of a gene can be caused, for example, by using a recombinant gene engineered to contain an insertional mutation (*e.g.*, the *neo* gene). The recombinant gene is inserted into the genome of a recipient cell, tissue or animal, and inactivates transcription of the receptor. Such a construct may be introduced into a cell, such as an embryonic stem cell, by techniques such as transfection, transduction, and injection. Stem cells lacking an intact receptor sequence may generate transgenic animals deficient in the receptor.

Preferred test models are transgenic animals. A transgenic animal has cells containing DNA which has been artificially inserted into a cell and inserted into the genome of the animal which develops from that cell. Preferred transgenic animals are primates, mice, rats, cows, pigs, horses, goats, sheep, dogs and cats.

A variety of methods are available for producing transgenic animals. For example, DNA can be injected into the pronucleus of a fertilized egg before fusion of the male and female pronuclei, or injected into the nucleus of an embryonic cell (*e.g.*, the nucleus of a two-cell embryo) following the initiation of cell division (Brinster *et al.*, *Proc. Nat. Acad. Sci. USA 82*: 4438-4442, 1985). By way of another example, embryos can be infected with viruses, especially retroviruses, modified to carry $GABA_BR2$ nucleotide sequences.

Pluripotent stem cells derived from the inner cell mass of the embryo and stabilized in culture can be manipulated in culture to incorporate nucleotide sequences of the invention. A transgenic animal can be produced from such stem cells through implantation into a blastocyst that is implanted into a foster mother and allowed to come to term. Animals suitable for transgenic experiments can be obtained from standard commercial sources such as Charles River (Wilmington, MA), Taconic (Germantown, NY), and Harlan Sprague Dawley (Indianapolis, IN).

Methods for the culturing of embryonic stem (ES) cells and the subsequent production of transgenic animals by the introduction of DNA into ES cells using methods such as electroporation, calcium phosphate/DNA precipitation and direct injection are well known to those of ordinary skill in the art. See, for example, Teratocarcinomas and Embryonic Stem Cells, A Practical Approach, E.J. Robertson, ed., IRL Press (1987).

Procedures for embryo manipulations are well known in the art. Procedures for manipulating rodent embryo and for microinjecting DNA into the pronucleus of the zygote are well known in the art. Microinjection procedures for fish, amphibian eggs and birds are well known in the art and are described, for example, in Houdebine and Chourrout, *Experientia* 47: 897-905, 1991. Procedures for introducing DNA into tissues of animals are well known in the art and are described, for example, in U.S. Patent No. 4,945,050.

Transfection and isolation of desired clones can be carried out using standard techniques (*e.g.*, E.J. Robertson, *supra*). For example, random gene integration can be carried out by co-transfecting nucleic acid with a gene encoding antibiotic resistance. Alternatively, for example, the gene encoding antibiotic resistance is physically linked to a nucleic acid sequence encoding $GABA_BR2$.

DNA molecules introduced into ES cells can also be integrated into the chromosome through the process of homologous recombination. (*E.g.*, Capecchi, *Science 244*: 1288-1292, 1989.) Methods for positive selection of the recombination event (*e.g.*, neomycin resistance) and dual positive-negative selection (*e.g.*, neomycin resistance and gancyclovir resistance) and the subsequent identification of the desired clones by PCR have been described in references such as Capecchi, *supra* and Joyner *et al.*, *Nature 338*:153-156, 1989, which is hereby incorporated by reference herein.

The final phase of the procedure is to inject targeted ES cells into blastocysts and to transfer the blastocysts into pseudopregnant females. The resulting chimeric animals are bred and the offspring are analyzed by Southern blotting to identify individuals carrying the transgene.

An example describing the preparation of a transgenic mouse

is as follows. Female mice are induced to superovulate and placed with males. The mated females are sacrificed by CO_2 asphyxiation or cervical dislocation and embryos are recovered from excised oviducts. Surrounding cumulus cells are removed. Pronuclear embryos are then washed and stored until the time of injection.

Randomly cycling adult female mice paired with vasectomized males serve as recipients for implanted embryos. Recipient females are mated at the same time as donor females and embryos are transferred surgically to recipient females.

Procedures for generating transgenic rats are similar to that of mice. (*E.g.*, Hammer *et al.*, Cell 63:1099-1112, 1990.) Procedures for producing transgenic non-rodent mammals and other animals are well known in art. (*E.g.*, Houdebine and Chourrout, *supra*; Pursel *et al.*, *Science 244*:1281-1288, 1989; and Simms *et al.*, *Bio/Technology* 6:179-183, 1988.)

Therapeutic Modulation

Different types of diseases and disorders can be treated using compounds modulating $GABA_BR$ activity. Additionally, such compounds can be used prophylactically. Compounds modulating $GABA_BR$ activity can be administered to patients who would benefit from such treatment. Patients are mammals, preferably humans.

Modulating $GABA_BR$ activity can be carried to achieve useful therapeutic effects such as preventing or treating one or more of the following: spasticity and motor control disorders using $GABA_BR$ agonists; pain, using $GABA_BR$ antagonists; cognitive disorders using $GABA_BR$ antagonists; neurological disorders such as Alzheimer's disease and Huntington's disease; psychiatric disorders, such as depression using $GABA_BR$ agonists; alcohol dependence and withdrawal using $GABA_BR$ antagonists; feeding behavior; cardiovascular and respiratory disorders with antagonists exerting an excitatory effect and agonists depressing inspiratory neurons; and peripheral function disorders.

Modulators of $GABA_BR$ activity can be administered to a patient using standard techniques. Techniques and formulations generally may be found in Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing Co., Easton, PA, 1990 (hereby incorporated by reference herein).

Suitable dosage forms, in part, depend upon the use or the route of entry, for example, oral, transdermal, transmucosal, or by injection (parenteral). Such dosage forms should allow the therapeutic agent to reach a target cell whether the target cell is present in a multicellular host or in culture. For example, pharmacological compounds or compositions injected into the blood stream should be soluble. Other factors are well known in the art, and include considerations such as toxicity and dosage forms which retard the therapeutic agent from exerting its effect.

Therapeutic compounds can be formulated as pharmaceutically acceptable salts and complexes thereof. Pharmaceutically acceptable salts are non-toxic salts in the amounts and concentrations at which they are administered. The preparation of such salts can facilitate the pharmacological use by altering the physical characteristics of the compound without preventing it from exerting its physiological effect. Useful alterations in physical properties include lowering the melting point to facilitate transmucosal administration and increasing the solubility to facilitate administering higher concentrations of the drug.

The pharmaceutically acceptable salt of a compound may be present as a complex. Examples of complexes include an 8-chlorotheophylline complex (analogous to, *e.g.*, dimenhydrinate:diphenhydramine 8-chlorotheophylline (1:1) complex; Dramamine) and various cyclodextrin inclusion complexes.

Pharmaceutically acceptable salts include acid addition salts such as those containing sulfate, hydrochloride, fumarate, maleate, phosphate, sulfamate, acetate, citrate, lactate, tartrate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, cyclohexylsulfamate and quinate.

Pharmaceutically acceptable salts can be obtained from acids such as hydrochloric acid, maleic acid, sulfuric acid, phosphoric acid, sulfamic acid, acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, cyclohexylsulfamic acid, fumaric acid, and quinic acid. Pharmaceutically acceptable salts also include basic addition salts such as those containing benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine,

aluminum, calcium, lithium, magnesium, potassium, sodium, ammonium, alkylamine, and zinc, when acidic functional groups, such as carboxylic acid or phenol are present. For example, see Remington's Pharmaceutical Sciences, 18^{th} ed., Mack Publishing Co., Easton, PA, p. 1445, 1990. Such salts can be prepared using the appropriate corresponding bases.

Carriers or excipients can also be used to facilitate administration of therapeutic agents. Examples of carriers include calcium carbonate, calcium phosphate, various sugars such as lactose, glucose, or sucrose, or types of starch, cellulose derivatives, gelatin, vegetable oils, polyethylene glycols and physiologically compatible solvents. Examples of physiologically compatible solvents include sterile solutions of water for injection (WFI), saline solution and dextrose.

$GABA_BR$ modulating compounds can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical (transdermal), or transmucosal administration. For systemic administration, oral administration is preferred. For oral administration, for example, the compounds can be formulated into conventional oral dosage forms such as capsules, tablets, and liquid preparations such as syrups, elixirs, and concentrated drops.

Alternatively, injection (parenteral administration) may be used, *e.g.*, intramuscular, intravenous, intraperitoneal, and subcutaneous. For injection, compounds are formulated in liquid solutions, preferably, in physiologically compatible buffers or solutions, such as saline solution, Hank's solution, or Ringer's solution. In addition, the compounds may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms can also be produced.

Systemic administration can be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are well known in the art, and include, for example, for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration, for example, may be through nasal sprays, rectal suppositories, or vaginal suppositories.

For topical administration, compounds can be formulated into ointments, salves, gels, or creams, as is well known in the art.

The amounts of various $GABA_BR$ modulating compounds to be administered can be determined by standard procedures taking into account factors such as the compound IC_{50}, EC_{50}, the biological half-life of the compound, the age, size and weight of the patient, and the disease or disorder associated with the patient. The importance of these and other factors to be considered are well known to those of ordinary skill in the art. Generally, the amount is expected to preferably be between about 0.01 and 50 mg/kg of the animal to be treated.

EXAMPLES

The example provided below illustrates different aspects and embodiments of the present invention. The example is not intended to limit the claimed invention.

Functional expression of $GABA_BR2$

Xenopus oocytes were co-injected with *in vitro* transcribed RNA (7 ng) encoding $GABA_BR1a$, $GABA_BR2$ and chimeric Gqo5. Chimeric Gqo5 is described in *Nature 363*:274-276, 1993. Coexpression of the different proteins was employed because $GABA_BR$ functions as a heterodimer of the subunits $GABA_BR1$ or $GABA_BR2$ (Jones *et al. Nature 396*:674-679, 1998). Following a 72 hour incubation, the oocytes were voltage clamped using standard electrophysiological techniques (Hille, B., Ionic Channels of Excitable membranes, pp. 30-33, Sinauer Associates, Inc., Sunderland, MA, 1992). Activation of the receptor heterodimers was detected by increases in the calcium-activated chloride current.

Application of the $GABA_B$ receptor agonist baclofen caused dose-dependent, reversible, oscillatory increases in the calcium-activated chloride current as shown in Figure 4, with an EC_{50} of approximately 1 µM. These responses were completely blocked by the competitive $GABA_B$ receptor antagonist SCH 50911 (100 µM). Oocytes expressing $GABA_B$ receptor heterodimers with the inwardly rectifying potassium channels (GIRKS; Kir3.1/3.2/3.4) were used as the positive control (Jones *et al., Nature 396*:674-679, 1998.) Thus, the use of the chimeric G-Protein Gqo5 promotes signal transduction through mobilization of intracellular calcium.

Other embodiments are within the following claims. Thus, while several embodiments have been shown and described, various modifications may be made, without departing from the spirit and scope of the present invention.

Claims

1. A purified nucleic acid comprising at least 18 contiguous nucleotides of a nucleic acid sequence provided in SEQ ID NO: 1.

2. The purified nucleic acid of claim 1, comprising at least 27 contiguous nucleotides of the nucleic acid sequence provided in SEQ ID NO: 1.

3. The purified nucleic acid of claim 2, comprising at least 45 contiguous nucleotides of the nucleic acid sequence provided in SEQ ID NO: 1.

4. The purified nucleic acid of claim 3, comprising the nucleic acid sequence provided in SEQ ID NO: 1.

5. A purified nucleic acid comprising a nucleic acid sequence encoding at least 6 contiguous amino acids of an amino acid sequence provided in SEQ. ID. NO: 4.

6. The purified nucleic acid of claim 5, wherein said nucleic acid encodes at least 12 contiguous amino acids of the amino acid sequence provided in SEQ. ID. NO: 4.

7. The purified nucleic acid of claim 6, wherein said nucleic acid encodes at least 18 contiguous amino acids of the amino acid sequence provided in SEQ. ID. NO: 4.

8. The purified nucleic acid of claim 7, wherein said nucleic acid encodes at least 54 contiguous amino acids of the amino acid sequence provided in SEQ. ID. NO: 4.

9. The purified nucleic acid of claim 8, wherein said nucleic acid encodes the amino acid sequence provided in SEQ. ID. NO: 4.

10. The purified nucleic acid of any of claims 1-9, wherein said nucleic acid is substantially purified.

11. The purified nucleic acid of any of claims 1-9, wherein said nucleic acid is recombinant nucleic acid which is part of an expression vector.

12. The purified nucleic acid of any of claims 1-9, wherein said nucleic acid is transcriptionally coupled to an exogenous promoter.

13. A recombinant cell comprising the expression vector of claim 11.

14. A recombinant cell made by a process comprising the step of introducing the nucleic acid of any one of claims 1-12 into a cell.

15. A purified nucleic acid comprising a nucleotide sequence of 20 contiguous nucleotides of which at least 18 nucleotides are complementary to the nucleic acid sequence provided in SEQ ID NO: 1 or the perfect complement of SEQ ID NO: 1.

16. The nucleic acid of claim 15, wherein said purified nucleic acid comprises a nucleotide sequence of 20 contiguous nucleotides which has at least 19 bases complementary to the nucleic acid sequence provided in SEQ ID NO: 1 or the perfect complement of SEQ ID NO: 1.

17. The nucleic acid of claim 16, wherein said purified nucleic acid comprises a nucleotide sequence of 20 contiguous nucleotides which is complementary to the nucleic acid sequence provided in SEQ ID NO: 1 or the perfect complement of SEQ ID NO: 1.

18. A purified polypeptide comprising at least 6 contiguous amino acids of an amino acid sequence provided in SEQ. ID. NO: 4.

19. The purified polypeptide of claim 18, comprising at least 12 contiguous amino acids of the amino acid sequence

provided in SEQ. ID. NO: 4.

20. The purified polypeptide of claim 19, comprising at least 18 contiguous amino acids of the amino acid sequence provided in SEQ. ID. NO: 4.

21. The purified polypeptide of claim 20, comprising at least 54 contiguous amino acids of the amino acid sequence provided in SEQ. ID. NO: 4.

22. The purified polypeptide of claim 21, consisting of the amino acid sequence provided in SEQ. ID. NO: 4.

23. The polypeptide of any one of claims 18-22, wherein said polypeptide is substantially purified.

24. A purified $GABA_BR2$-binding agent comprising a molecule which binds to a polypeptide consisting of the amino acid sequence of SEQ. ID. NO: 4.

25. The binding agent of claim 24, wherein said binding agent is an antibody.

26. A method of making a $GABA_BR2$ or fragment thereof comprising the step of incubating the recombinant cells of claim 13 under conditions wherein the nucleic acid encoding for the $GABA_BR2$ is expressed.

27. The method of claim 26, further comprising the step of purifying said $GABA_BR2$ or fragment thereof.

28. A method of selecting for a compound modulating $GABA_BR$ activity comprising the steps of

a) contacting a recombinant cell functionally expressing $GABA_BR2$ with a first test compound; and

b) measuring the ability of said test compound to affect $GABA_BR$ activity to select for said compound modulating $GABA_BR$ activity.

29. The method of claim 28, wherein the ability of a plurality of different test compounds to affect $GABA_BR$ activity are tested to select for said compound modulating $GABA_BR$ activity.

30. A coexpression system comprising

a) a cell;

b) at least one of $GABA_BR1a$ and $GABA_BR1b$, which is present in said cell;

c) $GABA_BR2$, which is present in said cell; and

d) Gqo5, which is present in said cell.

31. A method of screening for one or more compounds active at $GABA_BR1a$, $GABA_BR1b$, or $GABA_BR2$ comprising the steps of contacting the coexpression system of claim 30 with at least one of said compounds and measuring the ability of said compounds to effect the mobilization of intracellular calcium.

32. The method of claim 31, wherein 10 or more compounds are individually tested for their ability to effect the mobilization of intracellular calcium over the course of 8 hours.

33. A transgenic nonhuman mammal comprising a nonhuman mammal and a recombinant nucleic acid encoding a polypeptide comprising 6 contiguous amino acids of an amino acid sequence provided in SEQ. ID. NO: 4.

ClustalW Formatted Alignments

SEQ. ID. NO.1 A T G G C T T C C C C G C G G A G C T C C G G G C
SEQ. ID. NO. 2 A T G T T G C T G C T G C T G C T A C T G G C G C
SEQ. ID. NO. 3 A T G G G G C C C G G G G C C C C T T T T G C C C

SEQ. ID. NO.1 A G C C C G G G C C G C G C C G C C G C C G C C A
SEQ. ID. NO. 2 C A C T C T T C C T C C G C C C C C C G G G C G C
SEQ. ID. NO. 3 G G G T G G G G T G G C C A C T G C C G C T T C T

SEQ. ID. NO.1 C C G C C G C C C G C G C G C C T G C T A C T G C
SEQ. ID. NO. 2 G G G C G G G G C G C A G A C C C C C A A C G C C
SEQ. ID. NO. 3 G G T T G T G A T G G C G G C A G G G G T G G C T

SEQ. ID. NO.1 T A C T G C T G C T G C C G C T G C T G C T G C C
SEQ. ID. NO. 2 A C C T C A G A A G G T T G C C A G A T C A T A C
SEQ. ID. NO. 3 C C G G T G T G G G C C T C C C A C T C C C C C C

SEQ. ID. NO.1 T C T G G C G C C C G G G G C C T G G G G C T G G
SEQ. ID. NO. 2 A C C C G C C C T G G G A A G G G G G C A T C A G
SEQ. ID. NO. 3 A T C T C C C G C G G C C T C A C T C G C G G G T

SEQ. ID. NO.1 G C G C G G G G C G C C C C C C G G C C G C C G C
SEQ. ID. NO. 2 G T A C C G G G G C C T G A C T C G G G A C C A G
SEQ. ID. NO. 3 C C C C C C G C A C C C C T C C T C A G A A C G G

SEQ. ID. NO.1 C C A G C A G C C C G C C G C T C T C C A T C A T
SEQ. ID. NO. 2 G T G A A G G C T A T C A A C T T C C T G C C A G
SEQ. ID. NO. 3 C G C G C A G T G T A C A T C G G G G C A C T G T

SEQ. ID. NO.1 G G G C C T C A T G C C G C T C A C C A A G G A G
SEQ. ID. NO. 2 T G G A C T A T G A G A T T G A G T A T G T G T G
SEQ. ID. NO. 3 T T C C C A T G A G C G G G G G C T G G C C A G G

SEQ. ID. NO.1 G T G G C C A A G G G C A G C A T C G G G C G C G
SEQ. ID. NO. 2 C C G G G G G G A G C G C G A G G T G G T G G G G
SEQ. ID. NO. 3 G G G C C A G G C C T G C C A G C C C G C G G T G

FIGURE 1A

SEQ. ID. NO.1 G T G T G C T C C C C G C C G T G G A A C T G G C
SEQ. ID. NO. 2 C C C A A G G T C C G C A A G T G C C T G G C C A
SEQ. ID. NO. 3 G A G A T G G C G C T G G A G G A C G T G A A T A

SEQ. ID. NO.1 C A T C G A G C A G A T C C G C A A C G A G T C A
SEQ. ID. NO. 2 A C G G C T C C T G G A C A G A T A T G G A C A C
SEQ. ID. NO. 3 G C C G C A G G G A C A T C C T G C C G G A C T A

SEQ. ID. NO.1 C T C C T G C G C C C C T A C T T C C T C G A C C
SEQ. ID. NO. 2 A C C C A G C C G C T G T G T C C G A A T C T G C
SEQ. ID. NO. 3 T G A G C T C A A G C T C A T C C A C C A C G A C

SEQ. ID. NO.1 T G C G G C T C T A T G A C A C G G A G T G C G A
SEQ. ID. NO. 2 T C C A A G T C T T A T T T G A C C C T G G A A A
SEQ. ID. NO. 3 A G C A A G T G T G A T C C A G G C C A A G C C A

SEQ. ID. NO.1 C A A C G C A A A A G G G T T G A A A G C C T T C
SEQ. ID. NO. 2 A T G G G A A G G T T T T C C T G A C G G G T G G
SEQ. ID. NO. 3 C C A A G T A C C T A T A T G A G C T G C T C T A

SEQ. ID. NO.1 T A C G A T G C A A T A A A A T A C G G G C C G A
SEQ. ID. NO. 2 G G A C C T C C C A G C T C T G G A C G G A G C C
SEQ. ID. NO. 3 C A A C G A C C C T A T C A A G A T C A T C C T T

SEQ. ID. NO.1 A C C A C T T G A T G G T G T T T G G A G G C G T
SEQ. ID. NO. 2 C G G G T G G A T T T C C G G T G T G A C C C C G
SEQ. ID. NO. 3 A T G C C T G G C T G C A G C T C T G T C T C C A

SEQ. ID. NO.1 C T G T C C A T C C G T C A C A T C C A T C A T T
SEQ. ID. NO. 2 A C T T C C A T C T G G T G G G C A G C T C C C G
SEQ. ID. NO. 3 C G C T G G T G G C T G A G G C T G C T A G G A T

SEQ. ID. NO.1 G C A G A G T C C C T C C A A G G C T G G A A T C
SEQ. ID. NO. 2 G A G C A T C T G T A G T C A G G G C C A G T G G
SEQ. ID. NO. 3 G T G G A A C C T C A T T G T G C T T T C C T A T

SEQ. ID. NO.1 T G G T G C A G C T T T C T T T T G C T G C A A C
SEQ. ID. NO. 2 A G C A C C C C C A A G C C C C A C T G C C A G G
SEQ. ID. NO. 3 G G C T C C A G C T C A C C A G C C C T G T C A A

FIGURE 1B

SEQ. ID. NO.1	C A C G C C T G T T C T A G C C G A T A A G A A A
SEQ. ID. NO. 2	T G A A T C G A A C G C C A C A C T C A G A A C G
SEQ. ID. NO. 3	A C C G G C A G C G T T T C C C C A C T T T C T T
SEQ. ID. NO.1	A A A T A C C C T T A T T T C T T T C G G A C C G
SEQ. ID. NO. 2	G C G C G C A G T G T A C A T C G G G G C A C T G
SEQ. ID. NO. 3	C C G A A C G C A C C C A T C A G C C A C A C T C
SEQ. ID. NO.1	T C C C A T C A G A C A A T G C G G T G A A T C C
SEQ. ID. NO. 2	T T T C C C A T G A G C G G G G G C T G G C C A G
SEQ. ID. NO. 3	C A C A A C C C T A C C C G C G T G A A A C T C T
SEQ. ID. NO.1	A G C C A T T C T G A A G T T G C T C A A G C A C
SEQ. ID. NO. 2	G G G G C C A G G C C T G C C A G C C C G C G G T
SEQ. ID. NO. 3	T T G A A A A G T G G G G C T G G A A G A A G A T
SEQ. ID. NO.1	T A C C A G T G G A A G C G C G T G G G C A C G C
SEQ. ID. NO. 2	G G A G A T G G C G C T G G A G G A C G T G A A T
SEQ. ID. NO. 3	T G C T A C C A T C C A G C A G A C C A C T G A G
SEQ. ID. NO.1	T G A C G C A A G A C G T T C A G A G G T T C T C
SEQ. ID. NO. 2	A G C C G C A G G G A C A T C C T G C C G G A C T
SEQ. ID. NO. 3	G T C T T C A C T T C G A C T C T G G A C G A C C
SEQ. ID. NO.1	T G A G G T G C G G A A T G A C C T G A C T G G A
SEQ. ID. NO. 2	A T G A G C T C A A G C T C A T C C A C C A C G A
SEQ. ID. NO. 3	T G G A G G A A C G A G T G A A G G A G G C T G G
SEQ. ID. NO.1	G T T C T G T A T G G C G A G G A C A T T G A G A
SEQ. ID. NO. 2	C A G C A A G T G T G A T C C A G G C C A A G C C
SEQ. ID. NO. 3	A A T T G A G A T T A C T T T C C G C C A G A G T
SEQ. ID. NO.1	T T T C A G A C A C C G A G A G C T T C T C C A A
SEQ. ID. NO. 2	A C C A A G T A C C T A T A T G A G C T G C T C T
SEQ. ID. NO. 3	T T C T T C T C A G A T C C A G C T G T G C C C G
SEQ. ID. NO.1	C G A T C C C T G T A C C A G T G T C A A A A A G
SEQ. ID. NO. 2	A C A A C G A C C C T A T C A A G A T C A T C C T
SEQ. ID. NO. 3	T C A A A A A C C T G A A G C G C C A G G A T G C

FIGURE 1C

SEQ. ID. NO.1	C T G A A G G G G A A T G A T G T G C G G A T C A
SEQ. ID. NO. 2	T A T G C C T G G C T G C A G C T C T G T C T C C
SEQ. ID. NO. 3	C C G A A T C A T C G T G G G A C T T T T C T A T
SEQ. ID. NO.1	T C C T T G G C C A G T T T G A C C A G A A T A T
SEQ. ID. NO. 2	A C G C T G G T G G C T G A G G C T G C T A G G A
SEQ. ID. NO. 3	G A G A C T G A A G C C C G G A A A G T T T T T T
SEQ. ID. NO.1	G G C A G C A A A A G T G T T C T G T T G T G C A
SEQ. ID. NO. 2	T G T G G A A C C T C A T T G T G C T T T C C T A
SEQ. ID. NO. 3	G T G A G G T G T A C A A G G A G C G T C T C T T
SEQ. ID. NO.1	T A C G A G G A G A A C A T G T A T G G T A G T A
SEQ. ID. NO. 2	T G G C T C C A G C T C A C C A G C C C T G T C A
SEQ. ID. NO. 3	T G G G A A G A A G T A C G T C T G G T T C C T C
SEQ. ID. NO.1	A A T A T C A G T G G A T C A T T C C G G G C T G
SEQ. ID. NO. 2	A A C C G G C A G C G T T T C C C C A C T T T C T
SEQ. ID. NO. 3	A T T G G G T G G T A T G C T G A C A A T T G G T
SEQ. ID. NO.1	G T A C G A G C C T T C T T G G T G G G A G C A G
SEQ. ID. NO. 2	T C C G A A C G C A C C C A T C A G C C A C A C T
SEQ. ID. NO. 3	T C A A G A T C T A C G A C C C T T C T A T C A A
SEQ. ID. NO.1	G T G C A C A C G G A A G C C A A C T C A T C C C
SEQ. ID. NO. 2	C C A C A A C C C T A C C C G C G T G A A A C T C
SEQ. ID. NO. 3	C T G C A C A G T G G A T G A G A T G A C T G A G
SEQ. ID. NO.1	G C T G C C T C C G G A A G A A T C T G C T T G C
SEQ. ID. NO. 2	T T T G A A A A G T G G G G C T G G A A G A A G A
SEQ. ID. NO. 3	G C G G T G G A G G G C C A C A T C A C A A C T G
SEQ. ID. NO.1	T G C C A T G G A G G G C T A C A T T G G C G T G
SEQ. ID. NO. 2	T T G C T A C C A T C C A G C A G A C C A C T G A
SEQ. ID. NO. 3	A G A T T G T C A T G C T G A A T C C T G C C A A
SEQ. ID. NO.1	G A T T T C G A G C C C C T G A G C T C C A A G C
SEQ. ID. NO. 2	G G T C T T C A C T T C G A C T C T G G A C G A C
SEQ. ID. NO. 3	T A C C C G C A G C A T T T C C A A C A T G A C A

FIGURE 1D

SEQ. ID. NO.1 A G A T C A A G A C C A T C T C A G G A A A G A C
SEQ. ID. NO. 2 C T G G A G G A A C G A G T G A A G G A G G C T G
SEQ. ID. NO. 3 T C C C A G G A A T T T G T G G A G A A A C T A A

SEQ. ID. NO.1 T C C A C A G C A G T A T G A G A G A G A G T A C
SEQ. ID. NO. 2 G A A T T G A G A T T A C T T T C C G C C A G A G
SEQ. ID. NO. 3 C C A A G C G A C T G A A A A G A C A C C C T G A

SEQ. ID. NO.1 A A C A A C A A G C G G T C A G G C G T G G G G C
SEQ. ID. NO. 2 T T T C T T C T C A G A T C C A G C T G T G C C C
SEQ. ID. NO. 3 G G A G A C A G G A G G C T T C C A G G A G G C A

SEQ. ID. NO.1 C C A G C A A G T T C C A C G G G T A C G C C T A
SEQ. ID. NO. 2 G T C A A A A A C C T G A A G C G C C A G G A T G
SEQ. ID. NO. 3 C C G C T G G C C T A T G A T G C C A T C T G G G

SEQ. ID. NO.1 C G A T G G C A T C T G G G T C A T C G C C A A G
SEQ. ID. NO. 2 C C C G A A T C A T C G T G G G A C T T T T C T A
SEQ. ID. NO. 3 C C T T G G C A C T G G C C C T G A A C A A G A C

SEQ. ID. NO.1 A C A C T G C A G A G G G C C A T G G A G A C A C
SEQ. ID. NO. 2 T G A G A C T G A A G C C C G G A A A G T T T T T
SEQ. ID. NO. 3 A T C T G G A G G A G G C G G C C G T T C T G G T

SEQ. ID. NO.1 T G C A T G C C A G C A G C C G G C A C C A G C G
SEQ. ID. NO. 2 T G T G A G G T G T A C A A G G A G C G T C T C T
SEQ. ID. NO. 3 G T G C G C C T G G A G G A C T T C A A C T A C A

SEQ. ID. NO.1 G A T C C A G G A C T T C A A C T A C A C G G A C
SEQ. ID. NO. 2 T T G G G A A G A A G T A C G T C T G G T T C C T
SEQ. ID. NO. 3 A C A A C C A G A C C A T T A C C G A C C A A A T

SEQ. ID. NO.1 C A C A C G C T G G G C A G G A T C A T C C T C A
SEQ. ID. NO. 2 C A T T G G G T G G T A T G C T G A C A A T T G G
SEQ. ID. NO. 3 C T A C C G G G C A A T G A A C T C T T C G T C C

SEQ. ID. NO.1 A T G C C A T G A A C G A G A C C A A C T T C T T
SEQ. ID. NO. 2 T T C A A G A T C T A C G A C C C T T C T A T C A
SEQ. ID. NO. 3 T T T G A G G G T G T C T C T G G C C A T G T G G

FIGURE 1E

SEQ. ID. NO.1	C G G G G T C A C G G G T C A A G T T G T A T T C
SEQ. ID. NO. 2	A C T G C A C A G T G G A T G A G A T G A C T G A
SEQ. ID. NO. 3	T G T T T G A T G C C A G C G G C T C T C G G A T
SEQ. ID. NO.1	C G G A A T G G G G A G A G A A T G G G G A C C A
SEQ. ID. NO. 2	G G C G G T G G A G G G C C A C A T C A C A A C T
SEQ. ID. NO. 3	G G C A T G G A C G C T T A T C G A G C A G C T T
SEQ. ID. NO.1	T T A A A T T T A C T C A A T T T C A A G A C A G
SEQ. ID. NO. 2	G A G A T T G T C A T G C T G A A T C C T G C C A
SEQ. ID. NO. 3	C A G G G T G G C A G C T A C A A G A A G A T T G
SEQ. ID. NO.1	C A G G G A G G T G A A G G T G G G A G A G T A C
SEQ. ID. NO. 2	A T A C C C G C A G C A T T T C C A A C A T G A C
SEQ. ID. NO. 3	G C T A C T A T G A C A G C A C C A A G G A T G A
SEQ. ID. NO.1	A A C G C T G T G G C C G A C A C A C T G G A G A
SEQ. ID. NO. 2	A T C C C A G G A A T T T G T G G A G A A A C T A
SEQ. ID. NO. 3	T C T T T C C T G G T C C A A A A C A G A T A A A
SEQ. ID. NO.1	T C A T C A A T G A C A C C A T C A G G T T C C A
SEQ. ID. NO. 2	A C C A A G C G A C T G A A A A G A C A C C C T G
SEQ. ID. NO. 3	T G G A T T G G A G G G T C C C C C C C A G C T G
SEQ. ID. NO.1	A G G A T C C G A A C C A C C A A A A G A C A A G
SEQ. ID. NO. 2	A G G A G A C A G G A G G C T T C C A G G A G G C
SEQ. ID. NO. 3	A C C A G A C C C T G G T C A T C A A G A C A T T
SEQ. ID. NO.1	A C C A T C A T C C T G G A G C A G C T G C G G A
SEQ. ID. NO. 2	A C C G C T G G C C T A T G A T G C C A T C T G G
SEQ. ID. NO. 3	C C G C T T C C T G T C A C A G A A A C T C T T T
SEQ. ID. NO.1	A G A T C T C C C T A C C T C T C T A C A G C A T
SEQ. ID. NO. 2	G C C T T G G C A C T G G C C C T G A A C A A G A
SEQ. ID. NO. 3	A T C T C C G T C T C A G T T C T C T C C A G C C
SEQ. ID. NO.1	C C T C T C T G C C C T C A C C A T C C T C G G G
SEQ. ID. NO. 2	C A T C T G G A G G A G G C G G C C G T T C T G G
SEQ. ID. NO. 3	T G G G C A T T G T C C T A G C T G T T G T C T G

FIGURE 1F

SEQ. ID. NO.1 A T G A T C A T G G C C A G T G C T T T T C T C T
SEQ. ID. NO. 2 T G T G C G C C T G G A G G A C T T C A A C T A C
SEQ. ID. NO. 3 T C T G T C C T T T A A C A T C T A C A A C T C A

SEQ. ID. NO.1 T C T T C A A C A T C A A G A A C C G G A A T C A
SEQ. ID. NO. 2 A A C A A C C A G A C C A T T A C C G A C C A A A
SEQ. ID. NO. 3 C A T G T C C G T T A T A T C C A G A A C T C A C

SEQ. ID. NO.1 G A A G C T C A T A A A G A T G T C G A G T C C A
SEQ. ID. NO. 2 T C T A C C G G G C A A T G A A C T C T T C G T C
SEQ. ID. NO. 3 A G C C C A A C C T G A A C A A C C T G A C T G C

SEQ. ID. NO.1 T A C A T G A A C A A C C T T A T C A T C C T T G
SEQ. ID. NO. 2 C T T T G A G G G T G T C T C T G G C C A T G T G
SEQ. ID. NO. 3 T G T G G G C T G C T C A C T G G C T T T A G C T

SEQ. ID. NO.1 G A G G G A T G C T C T C C T A T G C T T C C A T
SEQ. ID. NO. 2 G T G T T T G A T G C C A G C G G C T C T C G G A
SEQ. ID. NO. 3 G C T G T C T T C C C C C T G G G G C T C G A T G

SEQ. ID. NO.1 A T T T C T C T T T G G C C T T G A T G G A T C C
SEQ. ID. NO. 2 T G G C A T G G A C G C T T A T C G A G C A G C T
SEQ. ID. NO. 3 G T T A C C A C A T T G G G A G G A A C C A G T T

SEQ. ID. NO.1 T T T G T C T C T G A A A A G A C C T T T G A A A
SEQ. ID. NO. 2 T C A G G G T G G C A G C T A C A A G A A G A T T
SEQ. ID. NO. 3 T C C T T T C G T C T G C C A G G C C C G C C T C

SEQ. ID. NO.1 C A C T T T G C A C C G T C A G G A C C T G G A T
SEQ. ID. NO. 2 G G C T A C T A T G A C A G C A C C A A G G A T G
SEQ. ID. NO. 3 T G G C T C C T G G G C C T G G G C T T T A G T C

SEQ. ID. NO.1 T C T C A C C G T G G G C T A C A C G A C C G C T
SEQ. ID. NO. 2 A T C T T T C C T G G T C C A A A A C A G A T A A
SEQ. ID. NO. 3 T G G G C T A C G G T T C C A T G T T C A C C A A

SEQ. ID. NO.1 T T T G G G G C C A T G T T T G C A A A G A C C T
SEQ. ID. NO. 2 A T G G A T T G G A G G G T C C C C C C C A G C T
SEQ. ID. NO. 3 G A T T T G G T G G G T C C A C A C G G T C T T C

FIGURE 1G

SEQ. ID. NO.1	G G A G A G T C C A C G C C A T C T T C A A A A A
SEQ. ID. NO. 2	G A C C A G A C C C T G G T C A T C A A G A C A T
SEQ. ID. NO. 3	A C A A A G A A G G A A G A A A A G A A G G A G T
SEQ. ID. NO.1	T G T G A A A A T G A A G A A G A A G A T C A T C
SEQ. ID. NO. 2	T C C G C T T C C T G T C A C A G A A A C T C T T
SEQ. ID. NO. 3	G G A G G A A G A C T C T G G A A C C C T G G A A
SEQ. ID. NO.1	A A G G A C C A G A A A C T G C T T G T G A T C G
SEQ. ID. NO. 2	T A T C T C C G T C T C A G T T C T C T C C A G C
SEQ. ID. NO. 3	G C T G T A T G C C A C A G T G G G C C T G C T G
SEQ. ID. NO.1	T G G G G G G C A T G C T G C T G A T C G A C C T
SEQ. ID. NO. 2	C T G G G C A T T G T C C T A G C T G T T G T C T
SEQ. ID. NO. 3	G T G G G C A T G G A T G T C C T C A C T C T C G
SEQ. ID. NO.1	G T G T A T C C T G A T C T G C T G G C A G G C T
SEQ. ID. NO. 2	G T C T G T C C T T T A A C A T C T A C A A C T C
SEQ. ID. NO. 3	C C A T C T G G C A G A T C G T G G A C C C T C T
SEQ. ID. NO.1	G T G G A C C C C C T G C G A A G G A C A G T G G
SEQ. ID. NO. 2	A C A T G T C C G T T A T A T C C A G A A C T C A
SEQ. ID. NO. 3	G C A C C G G A C C A T T G A G A C A T T T G C C
SEQ. ID. NO.1	A G A A G T A C A G C A T G G A G C C G G A C C C
SEQ. ID. NO. 2	C A G C C C A A C C T G A A C A A C C T G A C T G
SEQ. ID. NO. 3	A A G G A G G A A C C T A A G G A A G A T A T T G
SEQ. ID. NO.1	A G C A G G A C G G G A T A T C T C C A T C C G C
SEQ. ID. NO. 2	C T G T G G G C T G C T C A C T G G C T T T A G C
SEQ. ID. NO. 3	A C G T C T C T A T T C T G C C C C A G C T G G A
SEQ. ID. NO.1	C C T C T C C T G G A G C A C T G T G A G A A C A
SEQ. ID. NO. 2	T G C T G T C T T C C C C C T G G G G C T C G A T
SEQ. ID. NO. 3	G C A T T G C A G C T C C A G G A A G A T G A A T
SEQ. ID. NO.1	C C C A T A T G A C C A T C T G G C T T G G C A T
SEQ. ID. NO. 2	G G T T A C C A C A T T G G G A G G A A C C A G T
SEQ. ID. NO. 3	A C A T G G C T T G G C A T T T T C T A T G G T T

FIGURE 1H

SEQ. ID. NO.1 C G T C T A T G C C T A C A A G G G A C T T C T C
SEQ. ID. NO. 2 T T C C T T T C G T C T G C C A G G C C C G C C T
SEQ. ID. NO. 3 A C A A G G G G C T G C T G C T G C T G C T G G G

SEQ. ID. NO.1 A T G T T G T T C G G T T G T T T C T T A G C T T
SEQ. ID. NO. 2 C T G G C T C C T G G G C C T G G G C T T T A G T
SEQ. ID. NO. 3 A A T C T T C C T T G C T T A T G A G A C C A A G

SEQ. ID. NO.1 G G G A G A C C C G C A A C G T C A G C A T C C C
SEQ. ID. NO. 2 C T G G G C T A C G G T T C C A T G T T C A C C A
SEQ. ID. NO. 3 A G T G T G T C C A C T G A G A A G A T C A A T G

SEQ. ID. NO.1 C G C A C T C A A C G A C A G C A A G T A C A T C
SEQ. ID. NO. 2 A G A T T T G G T G G G T C C A C A C G G T C T T
SEQ. ID. NO. 3 A T C A C C G G G C T G T G G G C A T G G C T A T

SEQ. ID. NO.1 G G G A T G A G T G T C T A C A A C G T G G G G A
SEQ. ID. NO. 2 C A C A A A G A A G G A A G A A A A G A A G G A G
SEQ. ID. NO. 3 C T A C A A T G T G G C A G T C C T G T G C C T C

SEQ. ID. NO.1 T C A T G T G C A T C A T C G G G G C C G C T G T
SEQ. ID. NO. 2 T G G A G G A A G A C T C T G G A A C C C T G G A
SEQ. ID. NO. 3 A T C A C T G C T C C T G T C A C C A T G A T T C

SEQ. ID. NO.1 C T C C T T C C T G A C C C G G G A C C A G C C C
SEQ. ID. NO. 2 A G C T G T A T G C C A C A G T G G G C C T G C T
SEQ. ID. NO. 3 T G T C C A G C C A G C A G G A T G C A G C C T T

SEQ. ID. NO.1 A A T G T G C A G T T C T G C A T C G T G G C T C
SEQ. ID. NO. 2 G G T G G G C A T G G A T G T C C T C A C T C T C
SEQ. ID. NO. 3 T G C C T T T G C C T C T C T T G C C A T A G T T

SEQ. ID. NO.1 T G G T C A T C A T C T T C T G C A G C A C C A T
SEQ. ID. NO. 2 G C C A T C T G G C A G A T C G T G G A C C C T C
SEQ. ID. NO. 3 T T C T C C T C C T A T A T C A C T C T T G T T G

SEQ. ID. NO.1 C A C C C T C T G C C T G G T A T T C G T G C C G
SEQ. ID. NO. 2 T G C A C C G G A C C A T T G A G A C A T T T G C
SEQ. ID. NO. 3 T G C T C T T T G T G C C C A A G A T G C G C A G

FIGURE 1I

SEQ. ID. NO.1 A A G C T C A T C A C C C T G A G A A C A A A C C
SEQ. ID. NO. 2 C A A G G A G G A A C C T A A G G A A G A T A T T
SEQ. ID. NO. 3 G C T G A T C A C C C G A G G G G A A T G G C A G

SEQ. ID. NO.1 C A G A T G C A G C A A C G C A G A A C A G G C G
SEQ. ID. NO. 2 G A C G T C T C T A T T C T G C C C C A G C T G G
SEQ. ID. NO. 3 T C G G A G G C G C A G G A C A C C A T G A A G A

SEQ. ID. NO.1 A T T C C A G T T C A C T C A G A A T C A G A A G
SEQ. ID. NO. 2 A G C A T T G C A G C T C C A G G A A G A T G A A
SEQ. ID. NO. 3 C A G G G T C A T C G A C C A A C A A C A A C G A

SEQ. ID. NO.1 A A A G A A G A T T C T A A A A C G T C C A C C T
SEQ. ID. NO. 2 T A C A T G G C T T G G C A T T T T C T A T G G T
SEQ. ID. NO. 3 G G A G G A G A A G T C C C G G C T G T T G G A G

SEQ. ID. NO.1 C G G T C A C C A G T G T G A A C C A A G C C A G
SEQ. ID. NO. 2 T A C A A G G G G C T G C T G C T G C T G C T G G
SEQ. ID. NO. 3 A A G G A G A A C C G T G A A C T G G A A A A G A

SEQ. ID. NO.1 C A C A T C C C G C C T G G A G G G C C T A C A G
SEQ. ID. NO. 2 G A A T C T T C C T T G C T T A T G A G A C C A A
SEQ. ID. NO. 3 T C A T T G C T G A G A A A G A G G A G C G T G T

SEQ. ID. NO.1 T C A G A A A A C C A T C G C C T G C G A A T G A
SEQ. ID. NO. 2 G A G T G T G T C C A C T G A G A A G A T C A A T
SEQ. ID. NO. 3 C T C T G A A C T G C G C C A T C A A C T C C A G

SEQ. ID. NO.1 A G A T C A C A G A G C T G G A T A A A G A C T T
SEQ. ID. NO. 2 G A T C A C C G G G C T G T G G G C A T G G C T A
SEQ. ID. NO. 3 T C T C G G C A G C A G C T C C G C T C C C G G C

SEQ. ID. NO.1 G G A A G A G G T C A C C A T G C A G C T G C A G
SEQ. ID. NO. 2 T C T A C A A T G T G G C A G T C C T G T G C C T
SEQ. ID. NO. 3 G C C A C C C A C C G A C A C C C C C A G A A C C

SEQ. ID. NO.1 G A C A C A C C A G A A A A G A C C A C C T A C A
SEQ. ID. NO. 2 C A T C A C T G C T C C T G T C A C C A T G A T T
SEQ. ID. NO. 3 C T C T G G G G G C C T G C C C A G G G G A C C C

FIGURE 1J

SEQ. ID. NO.1 T T A A A C A G A A C C A C T A C C A A G A G C T
SEQ. ID. NO. 2 C T G T C C A G C C A G C A G G A T G C A G C C T
SEQ. ID. NO. 3 C C T G A G C C C C C C G A C C G G C T T A G C T

SEQ. ID. NO.1 C A A T G A C A T C C T C A A C C T G G G A A A C
SEQ. ID. NO. 2 T T G C C T T T G C C T C T C T T G C C A T A G T
SEQ. ID. NO. 3 G T G A T G G G A G T C G A G T G C A T T T G C T

SEQ. ID. NO.1 T T C A C T G A G A G C A C A G A T G G A G G A A
SEQ. ID. NO. 2 T T T C T C C T C C T A T A T C A C T C T T G T T
SEQ. ID. NO. 3 T T A T A A G T G A G G G T A G G G T G A G G G A

SEQ. ID. NO.1 A G G C C A T T T T A A A A A A T C A C C T C G A
SEQ. ID. NO. 2 G T G C T C T T T G T G C C C A A G A T G C G C A
SEQ. ID. NO. 3 G G A C A G G C C A G T A G G G G G A G G G A A A

SEQ. ID. NO.1 T C A A A A T C C C C A G C T A C A G T G G A A C
SEQ. ID. NO. 2 G G C T G A T C A C C C G A G G G G A A T G G C A
SEQ. ID. NO. 3 G G G A G A G G G G A A G G G C A G G G G A C T C

SEQ. ID. NO.1 A C A A C A G A G C C C T C T C G A A C A T G C A
SEQ. ID. NO. 2 G T C G G A G G C G C A G G A C A C C A T G A A G
SEQ. ID. NO. 3 A G G A A G C A G G G G G T C C C C A T C C C C A

SEQ. ID. NO.1 A A G A T C C T A T A G A A G A T A T A A A C T C
SEQ. ID. NO. 2 A C A G G G T C A T C G A C C A A C A A C A A C G
SEQ. ID. NO. 3 G C T G G G A A G A A C A T G C T A T C C A A T C

SEQ. ID. NO.1 T C C A G A A C A C A T C C A G C G T C G G C T G
SEQ. ID. NO. 2 A G G A G G A G A A G T C C C G G C T G T T G G A
SEQ. ID. NO. 3 T C A T C T C T T G T A A A T A C A T G T C C C C

SEQ. ID. NO.1 T C C C T C C A G C T C C C C A T C C T C C A C C
SEQ. ID. NO. 2 G A A G G A G A A C C G T G A A C T G G A A A A G
SEQ. ID. NO. 3 C T G T G A G T T C T G G G C T G A T T T G G G T

SEQ. ID. NO.1 A C G C C T A C C T C C C A T C C A T C G G A G G
SEQ. ID. NO. 2 A T C A T T G C T G A G A A A G A G G A G C G T G
SEQ. ID. NO. 3 C T C T C A T A C C T C T G G G A A A C A G A C C

FIGURE 1K

SEQ. ID. NO.1	C G T G G A C G C C A G C T G T G T C A G C C C C
SEQ. ID. NO. 2	T C T C T G A A C T G C G C C A T C A G C T C C A
SEQ. ID. NO. 3	T T T T T C T C T C T T A C T G C T T C A T G T A
SEQ. ID. NO.1	T G C G T C A G C C C C A C C G C C A G C C C C C
SEQ. ID. NO. 2	G T C T C G G C A G C A G C T C C G C T C C C G G
SEQ. ID. NO. 3	A T T T T G T A T C A C C T C T T C A C A A T T T
SEQ. ID. NO.1	G C C A C A G A C A T G T G C C A C C C T C C T T
SEQ. ID. NO. 2	C G C C A C C C A C C G A C A C C C C C A G A A C
SEQ. ID. NO. 3	A G T T C G T A C C T G G C T T G A A G C T G C T
SEQ. ID. NO.1	C C G A G T C A T G G T C T C G G G C C T G
SEQ. ID. NO. 2	C C T C T G G G G G C C T G C C C A G G G G A C C
SEQ. ID. NO. 3	C A C T G C T C A C A C G C T G C C T C C T C A G
SEQ. ID. NO.1	
SEQ. ID. NO. 2	C C C T G A G C C C C C C G A C C G G C T T A G C
SEQ. ID. NO. 3	C A G C C T C A C T G C A T C T T T C T C T T C C
SEQ. ID. NO.1	
SEQ. ID. NO. 2	T G T G A T G G G A G T C G A G T G C A T T T G C
SEQ. ID. NO. 3	C A T G C A A C A C C C T C T T C T A G T T A C C
SEQ. ID. NO.1	
SEQ. ID. NO. 2	T T T A T A A G T G A G G G T A G G G T G A G G G
SEQ. ID. NO. 3	A C G G C A A C C C C T
SEQ. ID. NO.1	
SEQ. ID. NO. 2	A G G A C A G G C C A G T A G G G G G A G G G A A
SEQ. ID. NO. 3	
SEQ. ID. NO.1	
SEQ. ID. NO. 2	A G G G A G A G G G G A A G G G C A G G G G A C T
SEQ. ID. NO. 3	
SEQ. ID. NO.1	
SEQ. ID. NO. 2	C A G G A A G C A G G G G G T C C C C A T C C C C
SEQ. ID. NO. 3	

FIGURE 1L

SEQ. ID. NO.1
SEQ. ID. NO. 2 A G C T G G G A A G A A C A T G C T A T C C A A T
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 C T C A T C T C T T G T A A A T A C A T G T C C C
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 C C T G T G A G T T C T G G G C T G A T T T G G G
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 T C T C T C A T A C C T C T G G G A A A C A G A C
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 C T T T T T C T C T C T T A C T G C T T C A T G T
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 A A T T T T G T A T C A C C T C T T C A C A A T T
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 T A G T T C G T A C C T G G C T T G A A G C T G C
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 T C A C T G C T C A C A C G C T G C C T C C T C A
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 G C A G C C T C A C T G C A T C T T T C T C T T C
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 C C A T G C A A C A C C C T C T T C T A G T T A C
SEQ. ID. NO. 3

FIGURE 1M

SEQ. ID. NO.1
SEQ. ID. NO. 2 C A C G G C A A C C C C T G C A G C T C C T C T G
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 C C T T T G T G C T C T G T T C C T G T C C A G C
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 A G G G G T C T C C C A A C A A G T G C T C T T T
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 C C A C C C C A A A G G G G C C T C T C C T T T T
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 C T C C A C T G T C A T A A T C T C T T T C C A T
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 C T T A C T T G C C C T T C T A T A C T T T C T C
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 A C A T G T G G C T C C C C C T G A A T T T T G C
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 T T C C T T T G G G G A G C T C A T T C T T T C G
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 C C A A G G T C A C A T G C T C C C T T G C C T C
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 T G G C T C C G T G C A
SEQ. ID. NO. 3

FIGURE 1N

ClustalW Formatted Alignments

SEQ. ID. NO. 4	M A S P R S S G Q P G P X P P P P P P P A R L L L
SEQ. ID. NO. 5	M L L L L L V P L F L R P L G A G G A Q T P N A T
SEQ. ID. NO. 6	M G P G G P C T P V G W P L P L L L V M A A G V A
SEQ. ID. NO. 7	M L L L L L L A P L F L R P P G A G G A Q T P N A
SEQ. ID. NO. 8	M G P G A P F A R V G W P L P L L V V M A A G V A

SEQ. ID. NO. 4	L L L L P L L L P L A P G A W G W A R G A P R P P
SEQ. ID. NO. 5	S E G C Q I I H P P W E G G I R Y R G L T R D Q V
SEQ. ID. NO. 6	P V W A S H S P H L P R P H P R V P P H P S S E R
SEQ. ID. NO. 7	T S E G C Q I I H P P W E G G I R Y R G L T R D Q
SEQ. ID. NO. 8	P V W A S H S P H L P R P H S R V P P H P S S E R

SEQ. ID. NO. 4	P S S P - P L S I M G L M P L T K E V A K G S I G
SEQ. ID. NO. 5	K A I N F L P V D Y E I E Y V C R G E R E V V G P
SEQ. ID. NO. 6	R A V Y I G A L F P M S G G W P G G Q A C Q P A V
SEQ. ID. NO. 7	V K A I N F L P V D Y E I E Y V C R G E R E V V G
SEQ. ID. NO. 8	R A V Y I G A L F P M S G G W P G G Q A C Q P A V

SEQ. ID. NO. 4	R G V L P A V E L A I E Q I R N E - S L L R P Y F
SEQ. ID. NO. 5	K V R K C L A N G S W T D M D T P S R C V R I C S
SEQ. ID. NO. 6	E M A L E D V N S R R D I L P D Y E L K L I H H D
SEQ. ID. NO. 7	P K V R K C L A N G S W T D M D T P S R C V R I C
SEQ. ID. NO. 8	E M A L E D V N S R R D I L P D Y E L K L I H H D

SEQ. ID. NO. 4	L D L R L Y D T E C D N A K G L K A F Y D A I K Y
SEQ. ID. NO. 5	K S Y L T L E N G K V F L T G G D L P A L D G A R
SEQ. ID. NO. 6	S K C D P G Q A T K Y L Y E L L Y N D P I K I I L
SEQ. ID. NO. 7	S K S Y L T L E N G K V F L T G G D L P A L D G A
SEQ. ID. NO. 8	S K C D P G Q A T K Y L Y E L L Y N D P I K I I L

SEQ. ID. NO. 4	G P N H L M V F G G V C P S V T S I I A E S L Q G
SEQ. ID. NO. 5	V E F R C D P D F H L V G S S R S V C S Q G Q W S
SEQ. ID. NO. 6	M P G C S S V S T L V A E A A R M W N L I V L S Y
SEQ. ID. NO. 7	R V D F R C D P D F H L V G S S R S I C S Q G Q W
SEQ. ID. NO. 8	M P G C S S V S T L V A E A A R M W N L I V L S Y

SEQ. ID. NO. 4	W N L V Q L S F A A T T P V L A D K K K Y P Y F F
SEQ. ID. NO. 5	T P K P H C Q V N R T P H S E R R A V Y I G A L F
SEQ. ID. NO. 6	G S S S P A L S N R Q R F P T F F R T H P S A T L
SEQ. ID. NO. 7	S T P K P H C Q V N R T P H S E R R A V Y I G A L
SEQ. ID. NO. 8	G S S S P A L S N R Q R F P T F F R T H P S A T L

FIGURE 2A

SEQ. ID. NO. 4	R T V P S D N A V N P A I L K L L K H Y Q W K R V
SEQ. ID. NO. 5	P M S G G W P G G Q A C Q P A V E M A L E D V N S
SEQ. ID. NO. 6	H N P T R V K L F E K W G W K K I A T I Q Q T T E
SEQ. ID. NO. 7	F P M S G G W P G G Q A C Q P A V E M A L E D V N
SEQ. ID. NO. 8	H N P T R V K L F E K W G W K K I A T I Q Q T T E

SEQ. ID. NO. 4	G T L T Q D V Q R F S E V R N D L T G V L Y G E D
SEQ. ID. NO. 5	R R D I L P D Y E L K L I H H D S K C D P G Q A T
SEQ. ID. NO. 6	V F T S T L D D L E E R V K E A G I E I T F R Q S
SEQ. ID. NO. 7	S R R D I L P D Y E L K L I H H D S K C D P G Q A
SEQ. ID. NO. 8	V F T S T L D D L E E R V K E A G I E I T F R Q S

SEQ. ID. NO. 4	I E I S D T E S F S N D P C T S V K K L K G N D V
SEQ. ID. NO. 5	K Y L Y E L L Y N D P I K I I L M P G C S S V S T
SEQ. ID. NO. 6	F F S D P A V P V K N L K R Q D A R I I V G L F Y
SEQ. ID. NO. 7	T K Y L Y E L L Y N D P I K I I L M P G C S S V S
SEQ. ID. NO. 8	F F S D P A V P V K N L K R Q D A R I I V G L F Y

SEQ. ID. NO. 4	R I I L G Q F D Q N M A A K V F C C A Y E E N M Y
SEQ. ID. NO. 5	L V A E A A R M W N L I V L S Y G S S S P A L S N
SEQ. ID. NO. 6	E T E A R K V F C E V Y K E R L F G K K Y V W F L
SEQ. ID. NO. 7	T L V A E A A R M W N L I V L S Y G S S S P A L S
SEQ. ID. NO. 8	E T E A R K V F C E V Y K E R L F G K K Y V W F L

SEQ. ID. NO. 4	G S K Y Q W I I P G W Y E P S W W E Q V H T E A N
SEQ. ID. NO. 5	R Q R F P T F F R T H P S A T L H N P T R V K L F
SEQ. ID. NO. 6	I G W Y A D N W F K T Y D P S I N C T V E E M T E
SEQ. ID. NO. 7	N R Q R F P T F F R T H P S A T L H N P T R V K L
SEQ. ID. NO. 8	I G W Y A D N W F K I Y D P S I N C T V D E M T E

SEQ. ID. NO. 4	S S R C L R K N L L A A M E G Y I G V D F E P L S
SEQ. ID. NO. 5	E K W G W K K I A T I Q Q T T E V F T S T L D D L
SEQ. ID. NO. 6	A V E G H I T T E I V M L N P A N T R S I S N M T
SEQ. ID. NO. 7	F E K W G W K K I A T I Q Q T T E V F T S T L D D
SEQ. ID. NO. 8	A V E G H I T T E I V M L N P A N T R S I S N M T

SEQ. ID. NO. 4	S K Q I K T I S G K T P Q Q Y E R E Y N N K R S G
SEQ. ID. NO. 5	E E R V K E A G I E I T F R Q S F F S D P A V P V
SEQ. ID. NO. 6	S Q E F V E K L T K R L K R H P E E T G G F Q E A
SEQ. ID. NO. 7	L E E R V K E A G I E I T F R Q S F F S D P A V P
SEQ. ID. NO. 8	S Q E F V E K L T K R L K R H P E E T G G F Q E A

FIGURE 2B

SEQ. ID. NO. 4 V G P S K F H G Y A Y D G I W V I A K T L Q R A M
SEQ. ID. NO. 5 K N L K R Q D A R I I V G L F Y E T E A R K V F C
SEQ. ID. NO. 6 P L A Y D A I W A L A L A L N K T S G G G G R S G
SEQ. ID. NO. 7 V K N L K R Q D A R I I V G L F Y E T E A R K V F
SEQ. ID. NO. 8 P L A Y D A I W A L A L A L N K T S G G G G R S G

SEQ. ID. NO. 4 E T L H A S S R H Q R I Q D F N Y T D H T L G R I
SEQ. ID. NO. 5 E V Y K E R L F G K K Y V W F L I G W Y A D N W F
SEQ. ID. NO. 6 V R L E D F N Y N N Q T I T D Q I Y R A M N S S S
SEQ. ID. NO. 7 C E V Y K E R L F G K K Y V W F L I G W Y A D N W
SEQ. ID. NO. 8 V R L E D F N Y N N Q T I T D Q I Y R A M N S S S

SEQ. ID. NO. 4 I L N A M N E T N F F G V T G Q V V F R N G E R M
SEQ. ID. NO. 5 K T Y D P S I N C T V E E M T E A V E G H I T T E
SEQ. ID. NO. 6 F E G V S G H V V F D A S G S R M A W T L I E Q L
SEQ. ID. NO. 7 F K I Y D P S I N C T V D E M T E A V E G H I T T
SEQ. ID. NO. 8 F E G V S G H V V F D A S G S R M A W T L I E Q L

SEQ. ID. NO. 4 G T I K F T Q F Q D S R E V K V G E Y N A V A D T
SEQ. ID. NO. 5 I V M L N P A N T R S I S N M T S Q E F V E K L T
SEQ. ID. NO. 6 Q G G S Y K K I G Y Y D S T K D D L S W S K T D K
SEQ. ID. NO. 7 E I V M L N P A N T R S I S N M T S Q E F V E K L
SEQ. ID. NO. 8 Q G G S Y K K I G Y Y D S T K D D L S W S K T D K

SEQ. ID. NO. 4 L E I I N D T I R F Q G S E P P K D K T I I L E Q
SEQ. ID. NO. 5 K R L K R H P E E T G G F Q E A P L A Y D A I W A
SEQ. ID. NO. 6 W I G G S P P A D Q I L V I K T F R F L S Q K L F
SEQ. ID. NO. 7 T K R L K R H P E E T G G F Q E A P L A Y D A I W
SEQ. ID. NO. 8 W I G G S P P A D Q T L V I K T F R F L S Q K L F

SEQ. ID. NO. 4 L R K I S L P L Y S I L S A L T I L G M I M A S A
SEQ. ID. NO. 5 L A L A L N K T S G G G G R S G V R L E D F N Y N
SEQ. ID. NO. 6 I S V S V L S S L G I V L A V V C L S F N I Y N S
SEQ. ID. NO. 7 A L A L A L N K T S G G G G R S G V R L E D F N Y
SEQ. ID. NO. 8 I S V S V L S S L G I V L A V V C L S F N I Y N S

SEQ. ID. NO. 4 F L F F N I K N R N Q K L I K M S S P Y M N N L I
SEQ. ID. NO. 5 N Q T I T D Q I Y R A M N S S S F E G V S G H V V
SEQ. ID. NO. 6 H V R Y I Q N S Q P N L N N L T A V G C S L A L A
SEQ. ID. NO. 7 N N Q T I T D Q I Y R A M N S S S F E G V S G H V
SEQ. ID. NO. 8 H V R Y I Q N S Q P N L N N L T A V G C S L A L A

FIGURE 2C

SEQ. ID. NO. 4 I L G G M L S Y A S I F L F G L D G S F V S E K T
SEQ. ID. NO. 5 F D A S G S R M A W T L I E Q L Q G G S Y K K I G
SEQ. ID. NO. 6 A V F P L G L D G Y H I G R S Q F P F V C Q A R L
SEQ. ID. NO. 7 V F D A S G S R M A W T L I E Q L Q G G S Y K K I
SEQ. ID. NO. 8 A V F P L G L D G Y H I G R N Q F P F V C Q A R L

SEQ. ID. NO. 4 F E T L C T V R T W I L T V G Y T T A F G A M F A
SEQ. ID. NO. 5 Y Y D S T K D D L S W S K T D K W I G G S P P A D
SEQ. ID. NO. 6 W L L G L G F S L G Y G S M F T K I W W V H T V F
SEQ. ID. NO. 7 G Y Y D S T K D D L S W S K T D K W I G G S P P A
SEQ. ID. NO. 8 W L L G L G F S L G Y G S M F T K I W W V H T V F

SEQ. ID. NO. 4 K T W R V H A I F K N V K M K K K I I K D Q K L L
SEQ. ID. NO. 5 Q I L V I K T F R F L S Q K L F I S V S V L S S L
SEQ. ID. NO. 6 T K K E E K K E W R K T L E P W K L Y A T V G L L
SEQ. ID. NO. 7 D Q T L V I K T F R F L S Q K L F I S V S V L S S
SEQ. ID. NO. 8 T K K E E K K E W R K T L E P W K L Y A T V G L L

SEQ. ID. NO. 4 V I V G G M L L I D L C I L I C W Q A V D P L R R
SEQ. ID. NO. 5 G I V L A V V C L S F N I Y N S H V R Y I Q N S Q
SEQ. ID. NO. 6 V G M D V L T L A I W Q I V D P L H R T I E T F A
SEQ. ID. NO. 7 L G I V L A V V C L S F N I Y N S H V R Y I Q N S
SEQ. ID. NO. 8 V G M D V L T L A I W Q I V D P L H R T I E T F A

SEQ. ID. NO. 4 T V E K Y S M E P D P A G R D I S I R P L L E H C
SEQ. ID. NO. 5 P N L N N L T A V G C S L A L A A V F P L G L D G
SEQ. ID. NO. 6 K E E P K E D I D V S I L P Q L E H C S S K K M N
SEQ. ID. NO. 7 Q P N L N N L T A V G C S L A L A A V F P L G L D
SEQ. ID. NO. 8 K E E P K E D I D V S I L P Q L E H C S S R K M N

SEQ. ID. NO. 4 E N T H M T I W L G I V Y A Y K G L L M L F G C F
SEQ. ID. NO. 5 Y H I G R S Q F P F V C Q A R L W L L G L G F S L
SEQ. ID. NO. 6 T W L G I F Y G Y K G L L L L L G I F L A Y E T K
SEQ. ID. NO. 7 G Y H I G R N Q F P F V C Q A R L W L L G L G F S
SEQ. ID. NO. 8 T W L G I F Y G Y K G L L L L L G I F L A Y E T K

SEQ. ID. NO. 4 L A W E T R N V S I P A L N D S K Y I G M S V Y N
SEQ. ID. NO. 5 G Y G S M F T K I W W V H T V F T K K E E K K E W
SEQ. ID. NO. 6 S V S T E K I N D H R A V G M A I Y N V A V L C L
SEQ. ID. NO. 7 L G Y G S M F T K I W W V H T V F T K K E E K K E
SEQ. ID. NO. 8 S V S T E K I N D H R A V G M A I Y N V A V L C L

FIGURE 2D

SEQ. ID. NO. 4 V G I M C I I G A A V S F L T R D Q P N V Q F C I
SEQ. ID. NO. 5 R K T L E P W K L Y A T V G L L V G M D V L T L A
SEQ. ID. NO. 6 I T A P V T M I L S S Q Q D A A F A F A S L A I V
SEQ. ID. NO. 7 W R K T L E P W K L Y A T V G L L V G M D V L T L
SEQ. ID. NO. 8 I T A P V T M I L S S Q Q D A A F A F A S L A I V

SEQ. ID. NO. 4 V A L V I I F C S T I T L C L V F V P K L I T L R
SEQ. ID. NO. 5 I W Q I V D P L H R T I E T F A K E E P K E D I D
SEQ. ID. NO. 6 F S S Y I T L V V L F V P K M R R L I T R G E W Q
SEQ. ID. NO. 7 A I W Q I V D P L H R T I E T F A K E E P K E D I
SEQ. ID. NO. 8 F S S Y I T L V V L F V P K M R R L I T R G E W Q

SEQ. ID. NO. 4 T N P D A A T Q N R R F Q F T Q N Q K K E D S K T
SEQ. ID. NO. 5 V S I L P Q L E H C S S K K M N T W L G I F Y G Y
SEQ. ID. NO. 6 S E T Q D T M K T G S S T N N N E E E K S R L L E
SEQ. ID. NO. 7 D V S I L P Q L E H C S S R K M N T W L G I F Y G
SEQ. ID. NO. 8 S E A Q D T M K T G S S T N N N E E E K S R L L E

SEQ. ID. NO. 4 S T S V T S V N Q A S T S R L E G L Q S E N H R L
SEQ. ID. NO. 5 K G L L L L L G I F L A Y E T K S V S T E K I N D
SEQ. ID. NO. 6 K E N R E L E K I I A E K E E R V S E L R H Q L Q
SEQ. ID. NO. 7 Y K G L L L L L G I F L A Y E T K S V S T E K I N
SEQ. ID. NO. 8 K E N R E L E K I I A E K E E R V S E L R H Q L Q

SEQ. ID. NO. 4 R M K I T E L D K D L E E V T M Q L Q D T P E K T
SEQ. ID. NO. 5 H R A V G M A I Y N V A V L C L I T A P V T M I L
SEQ. ID. NO. 6 S R Q Q L R S R R H P P T P P D P S G G L P R G P
SEQ. ID. NO. 7 D H R A V G M A I Y N V A V L C L I T A P V T M I
SEQ. ID. NO. 8 S R Q Q L R S R R H P P T P P E P S G G L P R G P

SEQ. ID. NO. 4 T Y I K Q N H Y Q E L N D I L N L G N F T E S T D
SEQ. ID. NO. 5 S S Q Q D A A F A F A S L A I V F S S Y I T L V V
SEQ. ID. NO. 6 S E P P D R L S C D G S R V H L L Y K
SEQ. ID. NO. 7 L S S Q Q D A A F A F A S L A I V F S S Y I T L V
SEQ. ID. NO. 8 P E P P D R L S C D G S R V H L L Y K

SEQ. ID. NO. 4 G G K A I L K N H L D Q N P Q L Q W N T T E P S R
SEQ. ID. NO. 5 L F V P K M R R L I T R G E W Q S E T Q D T M K T
SEQ. ID. NO. 6
SEQ. ID. NO. 7 V L F V P K M R R L I T R G E W Q S E A Q D T M K
SEQ. ID. NO. 8

FIGURE 2E

SEQ. ID. NO. 4	T C K D P I E D I N S P E H I Q R R L S L Q L P I
SEQ. ID. NO. 5	G S S T N N N E E E K S R L L E K E N R E L E K I
SEQ. ID. NO. 6	
SEQ. ID. NO. 7	T G S S T N N N E E E K S R L L E K E N R E L E K
SEQ. ID. NO. 8	

SEQ. ID. NO. 4	L H H A Y L P S I G G V D A S C V S P C V S P T A
SEQ. ID. NO. 5	I A E K E E R V S E L R H Q L Q S R Q Q L R S R R
SEQ. ID. NO. 6	
SEQ. ID. NO. 7	I I A E K E E R V S E L R H Q L Q S R Q Q L R S R
SEQ. ID. NO. 8	

SEQ. ID. NO. 4	S P R H R H V P P S F R V M V S G L
SEQ. ID. NO. 5	H P P T P P D P S G G L P R G P S E P P D R L S C
SEQ. ID. NO. 6	
SEQ. ID. NO. 7	R H P P T P P E P S G G L P R G P P E P P D R L S
SEQ. ID. NO. 8	

SEQ. ID. NO. 4	
SEQ. ID. NO. 5	D G S R V H L L Y K
SEQ. ID. NO. 6	
SEQ. ID. NO. 7	C D G S R V H L L Y K
SEQ. ID. NO. 8	

FIGURE 2F

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Cys Cys Trp Val Leu Leu Ala Leu Thr Trp His Thr Ser Ala Tyr Gly Pro Asp>

CAG CGA GCC CAA AAG AAG GGG GAC ATT ATC CTT GGG GGG CTC TTT CCT ATT CAT
Gln Arg Ala Gln Lys Lys Gly Asp Ile Ile Leu Gly Gly Leu Phe Pro Ile His>

TTT GGA GTA GCA GCT AAA GAT CAA GAT CTC AAA TCA AGG CCG GAG TCT GTG GAA
Phe Gly Val Ala Ala Lys Asp Gln Asp Leu Lys Ser Arg Pro Glu Ser Val Glu>

TGT ATC AGG TAT AAT TTC CGT GGG TTT CGC TGG TTA CAG GCT ATG ATA TTT GCC
Cys Ile Arg Tyr Asn Phe Arg Gly Phe Arg Trp Leu Gln Ala Met Ile Phe Ala>

ATA GAG GAG ATA AAC AGC AGC CCA GCC CTT CTT CCC AAC TTG ACG CTG GGA TAC
Ile Glu Glu Ile Asn Ser Ser Pro Ala Leu Leu Pro Asn Leu Thr Leu Gly Tyr>

AGG ATA TTT GAC ACT TGC AAC ACC GTT TCT AAG GCC TTG GAA GCC ACC CTG AGT
Arg Ile Phe Asp Thr Cys Asn Thr Val Ser Lys Ala Leu Glu Ala Thr Leu Ser>

TTT GTT GCT CAA AAC AAA ATT GAT TCT TTG AAC CTT GAT GAG TTC TGC AAC TGC
Phe Val Ala Gln Asn Lys Ile Asp Ser Leu Asn Leu Asp Glu Phe Cys Asn Cys>

TCA GAG CAC ATT CCC TCT ACG ATT GCT GTG GTG GGA GCA ACT GGC TCA GGC GTC
Ser Glu His Ile Pro Ser Thr Ile Ala Val Val Gly Ala Thr Gly Ser Gly Val>

TCC ACG GCA GTG GCA AAT CTG CTG GGG CTC TTC TAC ATT CCC CAG GTC AGT TAT
Ser Thr Ala Val Ala Asn Leu Leu Gly Leu Phe Tyr Ile Pro Gln Val Ser Tyr>

GCC TCC TCC AGC AGA CTC CTC AGC AAC AAG AAT CAA TTC AAG TCT TTC CTC CGA
Ala Ser Ser Ser Arg Leu Leu Ser Asn Lys Asn Gln Phe Lys Ser Phe Leu Arg>

ACC ATC CCC AAT GAT GAG CAC CAG GCC ACT GCC ATG GCA GAC ATC ATC GAG TAT
Thr Ile Pro Asn Asp Glu His Gln Ala Thr Ala Met Ala Asp Ile Ile Glu Tyr>

TTC CGC TGG AAC TGG GTG GGC ACA ATT GCA GCT GAT GAC GAC TAT GGG CGG CCG
Phe Arg Trp Asn Trp Val Gly Thr Ile Ala Ala Asp Asp Asp Tyr Gly Arg Pro>

GGG ATT GAG AAA TTC CGA GAG GAA GCT GAG GAA AGG GAT ATC TGC ATC GAC TTC
Gly Ile Glu Lys Phe Arg Glu Glu Ala Glu Glu Arg Asp Ile Cys Ile Asp Phe>

AGT GAA CTC ATC TCC CAG TAC TCT GAT GAG GAA GAG ATC CAG CAT GTG GTA GAG
Ser Glu Leu Ile Ser Gln Tyr Ser Asp Glu Glu Glu Ile Gln His Val Val Glu>

GTG ATT CAA AAT TCC ACG GCC AAA GTC ATC GTG GTT TTC TCC AGT GGC CCA GAT
Val Ile Gln Asn Ser Thr Ala Lys Val Ile Val Val Phe Ser Ser Gly Pro Asp>

FIGURE 3A

CTT GAG CCC CTC ATC AAG GAG ATT GTC CGG CGC AAT ATC ACG GGC AAG ATC TGG
Leu Glu Pro Leu Ile Lys Glu Ile Val Arg Arg Asn Ile Thr Gly Lys Ile Trp>

CTG GCC AGC GAG GCC TGG GCC AGC TCC TCC CTG ATC GCC ATG CCT CAG TAC TTC
Leu Ala Ser Glu Ala Trp Ala Ser Ser Ser Leu Ile Ala Met Pro Gln Tyr Phe>

CAC GTG GTT GGC GGC ACC ATT GGA TTC GCT CTG AAG GCT GGG CAG ATC CCA GGC
His Val Val Gly Gly Thr Ile Gly Phe Ala Leu Lys Ala Gly Gln Ile Pro Gly>

TTC CGG GAA TTC CTG AAG AAG GTC CAT CCC AGG AAG TCT GTC CAC AAT GGT TTT
Phe Arg Glu Phe Leu Lys Lys Val His Pro Arg Lys Ser Val His Asn Gly Phe>

GCC AAG GAG TTT TGG GAA GAA ACA TTT AAC TGC CAC CTC CAA GAA GGT GCA AAA
Ala Lys Glu Phe Trp Glu Glu Thr Phe Asn Cys His Leu Gln Glu Gly Ala Lys>

GGA CCT TTA CCT GTG GAC ACC TTT CTG AGA GGT CAC GAA GAA AGT GGC GAC AGG
Gly Pro Leu Pro Val Asp Thr Phe Leu Arg Gly His Glu Glu Ser Gly Asp Arg>

TTT AGC AAC AGC TCG ACA GCC TTC CGA CCC CTC TGT ACA GGG GAT GAG AAC ATC
Phe Ser Asn Ser Ser Thr Ala Phe Arg Pro Leu Cys Thr Gly Asp Glu Asn Ile>

AGC AGT GTC GAG ACC CCT TAC ATA GAT TAC ACG CAT TTA CGG ATA TCC TAC AAT
Ser Ser Val Glu Thr Pro Tyr Ile Asp Tyr Thr His Leu Arg Ile Ser Tyr Asn>

GTG TAC TTA GCA GTC TAC TCC ATT GCC CAC GCC TTG CAA GAT ATA TAT ACC TGC
Val Tyr Leu Ala Val Tyr Ser Ile Ala His Ala Leu Gln Asp Ile Tyr Thr Cys>

TTA CCT GGG AGA GGG CTC TTC ACC AAT GGC TCC TGT GCA GAC ATC AAG AAA GTT
Leu Pro Gly Arg Gly Leu Phe Thr Asn Gly Ser Cys Ala Asp Ile Lys Lys Val>

GAG GCG TGG CAG GTC CTG AAG CAC CTA CGG CAT CTA AAC TTT ACA AAC AAT ATG
Glu Ala Trp Gln Val Leu Lys His Leu Arg His Leu Asn Phe Thr Asn Asn Met>

GGG GAG CAG GTG ACC TTT GAT GAG TGT GGT GAC CTG GTG GGG AAC TAT TCC ATC
Gly Glu Gln Val Thr Phe Asp Glu Cys Gly Asp Leu Val Gly Asn Tyr Ser Ile>

ATC AAC TGG CAC CTC TCC CCA GAG GAT GGC TCC ATC GTG TTT AAG GAA GTC GGG
Ile Asn Trp His Leu Ser Pro Glu Asp Gly Ser Ile Val Phe Lys Glu Val Gly>

TAT TAC AAC GTC TAT GCC AAG AAG GGA GAA AGA CTC TTC ATC AAC GAG GAG AAA
Tyr Tyr Asn Val Tyr Ala Lys Lys Gly Glu Arg Leu Phe Ile Asn Glu Glu Lys>

ATC CTG TGG AGT GGG TTC TCC AGG GAG GTG CCC TTC TCC AAC TGC AGC CGA GAC
Ile Leu Trp Ser Gly Phe Ser Arg Glu Val Pro Phe Ser Asn Cys Ser Arg Asp>

TGC CTG GCA GGG ACC AGG AAA GGG ATC ATT GAG GGG GAG CCC ACC TGC TGC TTT
Cys Leu Ala Gly Thr Arg Lys Gly Ile Ile Glu Gly Glu Pro Thr Cys Cys Phe>

GAG TGT GTG GAG TGT CCT GAT GGG GAG TAT AGT GAT GAG ACA GAT GCC AGT GCC
Glu Cys Val Glu Cys Pro Asp Gly Glu Tyr Ser Asp Glu Thr Asp Ala Ser Ala>

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FIGURE 3B

TGT AAC AAG TGC CCA GAT GAC TTC TGG TCC AAT GAG AAC CAC ACC TCC TGC ATT
Cys Asn Lys Cys Pro Asp Asp Phe Trp Ser Asn Glu Asn His Thr Ser Cys Ile>

GCC AAG GAG ATC GAG TTT CTG TCG TGG ACG GAG CCC TTT GGG ATC GCA CTC ACC
Ala Lys Glu Ile Glu Phe Leu Ser Trp Thr Glu Pro Phe Gly Ile Ala Leu Thr>

CTC TTT GCC GTG CTG GGC ATT TTC CTG ACA GCC TTT GTG CTG GGT GTG TTT ATC
Leu Phe Ala Val Leu Gly Ile Phe Leu Thr Ala Phe Val Leu Gly Val Phe Ile>

AAG TTC CGC AAC ACA CCC ATT GTC AAG GCC ACC AAC CGA GAG CTC TCC TAC CTC
Lys Phe Arg Asn Thr Pro Ile Val Lys Ala Thr Asn Arg Glu Leu Ser Tyr Leu>

CTC CTC TTC TCC CTG CTC TGC TGC TTC TCC AGC TCC CTG TTC TTC ATC GGG GAG
Leu Leu Phe Ser Leu Leu Cys Cys Phe Ser Ser Ser Leu Phe Phe Ile Gly Glu>

CCC CAG GAC TGG ACG TGC CGC CTG CGC CAG CCG GCC TTT GGC ATC AGC TTC GTG
Pro Gln Asp Trp Thr Cys Arg Leu Arg Gln Pro Ala Phe Gly Ile Ser Phe Val>

CTC TGC ATC TCA TGC ATC CTG GTG AAA ACC AAC CGT GTC CTC CTG GTG TTT GAG
Leu Cys Ile Ser Cys Ile Leu Val Lys Thr Asn Arg Val Leu Leu Val Phe Glu>

GCC AAG ATC CCC ACC AGC TTC CAC CGC AAG TGG TGG GGG CTC AAC CTG CAG TTC
Ala Lys Ile Pro Thr Ser Phe His Arg Lys Trp Trp Gly Leu Asn Leu Gln Phe>

CTG CTG GTT TTC CTC TGC ACC TTC ATG CAG ATT GTC ATC TGT GTG ATC TGG CTC
Leu Leu Val Phe Leu Cys Thr Phe Met Gln Ile Val Ile Cys Val Ile Trp Leu>

TAC ACC GCG CCC CCC TCA AGC TAC CGC AAC CAG GAG CTG GAG GAT GAG ATC ATC
Tyr Thr Ala Pro Pro Ser Ser Tyr Arg Asn Gln Glu Leu Glu Asp Glu Ile Ile>

TTC ATC ACG TGC CAC GAG GGC TCC CTC ATG GCC CTG GGC TTC CTG ATC GGC TAC
Phe Ile Thr Cys His Glu Gly Ser Leu Met Ala Leu Gly Phe Leu Ile Gly Tyr>

ACC TGC CTG CTG GCT GCC ATC TGC TTC TTC TTT GCC TTC AAG TCC CGG AAG CTG
Thr Cys Leu Leu Ala Ala Ile Cys Phe Phe Phe Ala Phe Lys Ser Arg Lys Leu>

CCG GAG AAC TTC AAT GAA GCC AAG TTC ATC ACC TTC AGC ATG CTC ATC TTC TTC
Pro Glu Asn Phe Asn Glu Ala Lys Phe Ile Thr Phe Ser Met Leu Ile Phe Phe>

ATC GTC TGG ATC TCC TTC ATT CCA GCC TAT GCC AGC ACC TAT GGC AAG TTT GTC
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TCT GCC GTA GAG GTG ATT GCC ATC CTG GCA GCC AGC TTT GGC TTG CTG GCG TGC
Ser Ala Val Glu Val Ile Ala Ile Leu Ala Ala Ser Phe Gly Leu Leu Ala Cys>

ATC TTC TTC AAC AAG ATC TAC ATC ATT CTC TTC AAG CCA TCC CGC AAC ACC ATC
Ile Phe Phe Asn Lys Ile Tyr Ile Ile Leu Phe Lys Pro Ser Arg Asn Thr Ile>

GAG GAG GTG CGT TGC AGC ACC GCA GCT CAC GCT TTC AAG GTG GCT GCC CGG GCC
Glu Glu Val Arg Cys Ser Thr Ala Ala His Ala Phe Lys Val Ala Ala Arg Ala>

ACG CTG CGC CGC AGC AAC GTC TCC CGC AAG CGG TCC AGC AGC CTT GGA GGC TCC
Thr Leu Arg Arg Ser Asn Val Ser Arg Lys Arg Ser Ser Ser Leu Gly Gly Ser>

FIGURE 3C

ACG GGA TCC ACC CCC TCC TCC TCC ATC AGC AGC AAG AGC AAC AGC GAA GAC CCA
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TTC CCA CAG CCC GAG AGG CAG AAG CAG CAG CAG CCG CTG GCC CTA ACC CAG CAA
Phe Pro Gln Pro Glu Arg Gln Lys Gln Gln Gln Pro Leu Ala Leu Thr Gln Gln>

GAG CAG CAG CAG CAG CCC CTG ACC CTC CCA CAG CAG CAA CGA TCT CAG CAG CAG
Glu Gln Gln Gln Gln Pro Leu Thr Leu Pro Gln Gln Gln Arg Ser Gln Gln Gln>

CCC AGA TGC AAG CAG AAG GTC ATC TTT GGC AGC GGC ACG GTC ACC TTC TCA CTG
Pro Arg Cys Lys Gln Lys Val Ile Phe Gly Ser Gly Thr Val Thr Phe Ser Leu>

AGC TTT GAT GAG CCT CAG AAG AAC GCC ATG GCC CAC GGG AAT TCT ACG CAC CAG
Ser Phe Asp Glu Pro Gln Lys Asn Ala Met Ala His Gly Asn Ser Thr His Gln>

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Asn Ser Leu Glu Ala Gln Lys Ser Ser Asp Thr Leu Thr Arg His Gln Pro Leu>

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Leu Pro Leu Gln Cys Gly Glu Thr Asp Leu Asp Leu Thr Val Gln Glu Thr Gly>

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Leu Gln Gly Pro Val Gly Gly Asp Gln Arg Pro Glu Val Glu Asp Pro Glu Glu>

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Leu Ser Pro Ala Leu Val Val Ser Ser Ser Gln Ser Phe Val Ile Ser Gly Gly>

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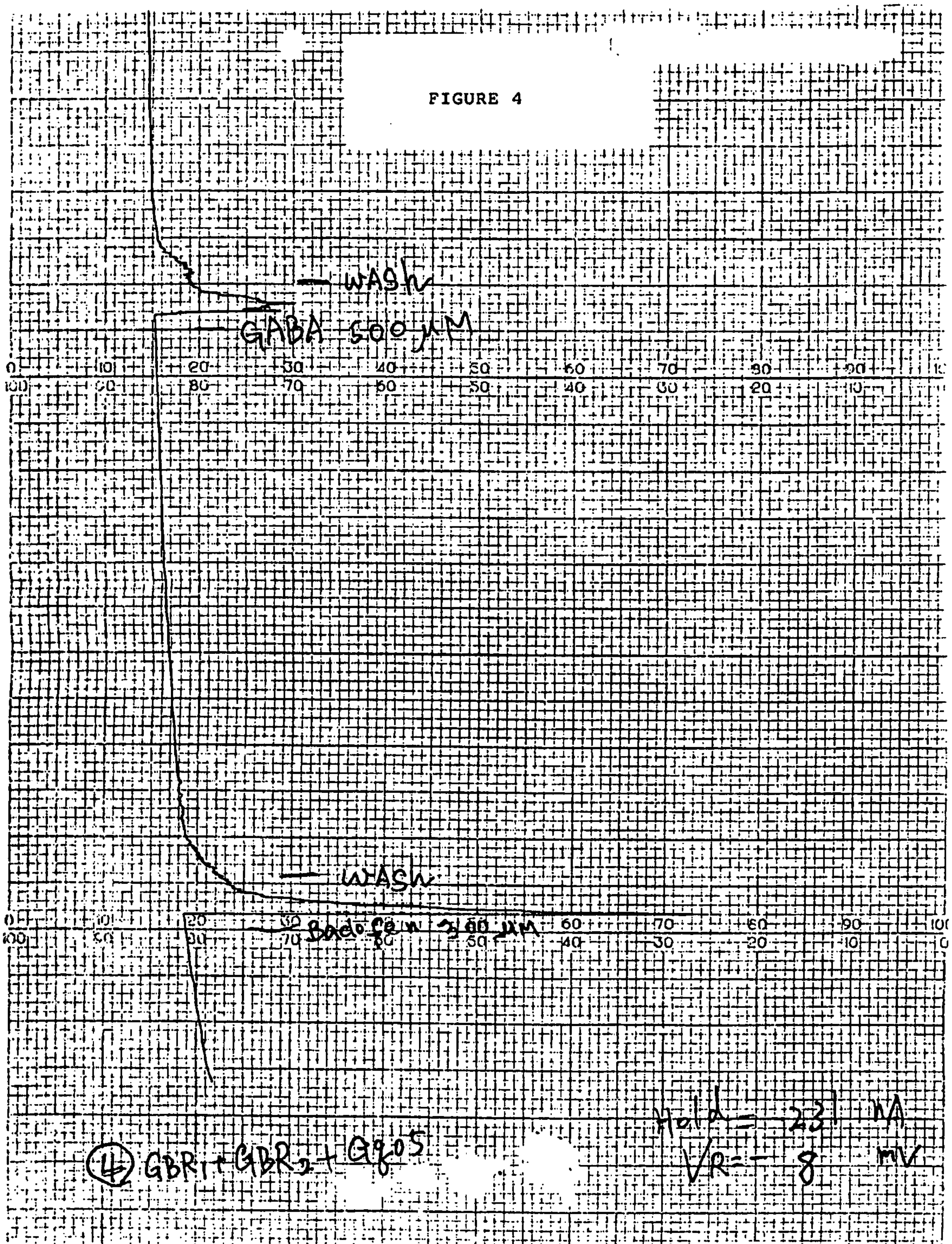
FIGURE 3D

FIGURE 4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WASH
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atcaagatca tccttatgcc tggctgcagc tctgtctcca cgctggtggc tgaggctgct    420
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gtgaaactct ttgaaaagtg ggctggaag aagattgcta ccatccagca gaccactgag     600
gtcttcactt cgactctgga cgacctggag gaacgagtga aggaggctgg aattgagatt    660
actttccgcc agagtttctt ctcagatcca gctgtgcccg tcaaaaacct gaagcgccag    720
gatgcccgaa tcatcgtggg acttttctat gagactgaag cccggaaagt tttttgtgag    780
gtgtacaagg agcgtctctt tgggaagaag tacgtctggt tcctcattgg gtggtatgct    840
gacaattggt tcaagatcta cgacccttct atcaactgca cagtggatga gatgactgag    900
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gcggtggagg gccacatcac aactgagatt gtcatgctga atcctgccaa tacccgcagc    960
atttccaaca tgacatccca ggaatttgtg gagaaactaa ccaagcgact gaaaagacac   1020
cctgaggaga caggaggctt ccaggaggca ccgctggcct atgatgccat ctgggccttg   1080
gcactggccc tgaacaagac atctggagga ggcggccgtt ctggtgtgcg cctggaggac   1140
ttcaactaca acaaccagac cattaccgac caaatctacc gggcaatgaa ctcttcgtcc   1200
tttgagggtg tctctggcca tgtggtgttt gatgccagcg gctctcggat ggcatggacg   1260
cttatcgagc agcttcaggg tggcagctac aagaagattg gctactatga cagcaccaag   1320
gatgatcttt cctggtccaa aacagataaa tggattggag ggtccccccc agctgaccag   1380
accctggtca tcaagacatt ccgcttcctg tcacagaaac tctttatctc cgtctcagtt   1440
ctctccagcc tgggcattgt cctagctgtt gtctgtctgt cctttaacat ctacaactca   1500
catgtccgtt atatccagaa ctcacagccc aacctgaaca acctgactgc tgtgggctgc   1560
tcactggctt tagctgctgt cttccccctg ggctcgatg  gttaccacat tgggaggaac   1620
cagtttcctt tcgtctgcca ggcccgcctc tggctcctgg gcctgggctt tagtctgggc   1680
tacggttcca tgttcaccaa gatttggtgg gtccacacgg tcttcacaaa gaaggaagaa   1740
aagaaggagt ggaggaagac tctggaaccc tggaagctgt atgccacagt gggcctgctg   1800
gtgggcatgg atgtcctcac tctcgccatc tggcagatcg tggaccctct gcaccggacc   1860
attgagacat ttgccaagga ggaacctaag gaagatattg acgtctctat tctgccccag   1920
ctggagcatt gcagctccag gaagatgaat acatggcttg gcattttcta tggttacaag   1980
gggctgctgc tgctgctggg aatcttcctt gcttatgaga ccaagagtgt gtccactgag   2040
aagatcaatg atcaccgggc tgtgggcatg gctatctaca atgtggcagt cctgtgcctc   2100
atcactgctc ctgtcaccat gattctgtcc agccagcagg atgcagcctt tgcctttgcc   2160
tctcttgcca tagttttctc ctcctatatc actcttgttg tgctctttgt gcccaagatg   2220
cgcaggctga tcacccgagg ggaatggcag tcggaggcgc aggacaccat gaagacaggg   2280
tcatcgacca acaacaacga ggaggagaag tcccggctgt tggagaagga gaaccgtgaa   2340
ctggaaaaga tcattgctga gaaagaggag cgtgtctctg aactgcgcca tcaactccag   2400
tctcggcagc agctccgctc ccggcgccac ccaccgacac cccagaacc  ctctgggggc   2460
ctgcccaggg gacccccctga gccccccgac cggcttagct gtgatgggag tcgagtgcat   2520
ttgctttata agtgagggta gggtgaggga ggacaggcca gtagggggag ggaaagggag   2580
aggggaaggg caggggactc aggaagcagg gggtccccat ccccagctgg gaagaacatg   2640
ctatccaatc tcatctcttg taaatacatg tccccctgtg agttctgggc tgatttgggt   2700
ctctcatacc tctgggaaac agaccttttt ctctcttact gcttcatgta attttgtatc   2760
acctcttcac aatttagttc gtacctggct tgaagctgct cactgctcac acgctgcctc   2820
ctcagcagcc tcactgcatc tttctcttcc catgcaacac cctcttctag ttaccacggc   2880
aacccct                                                             2887
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<210> 4
<211> 943
<212> PRT
<213> Human

<400> 4

Met Ala Ser Pro Arg Ser Ser Gly Gln Pro Gly Pro Xaa Pro Pro Pro
 1               5                  10                  15

Pro Pro Pro Pro Ala Arg Leu Leu Leu Leu Leu Leu Leu Pro Leu Leu
            20                  25                  30

Leu Pro Leu Ala Pro Gly Ala Trp Gly Trp Ala Arg Gly Ala Pro Arg
        35                  40                  45

Pro Pro Pro Ser Ser Pro Pro Leu Ser Ile Met Gly Leu Met Pro Leu
    50                  55                  60
```

```
Thr Lys Glu Val Ala Lys Gly Ser Ile Gly Arg Gly Val Leu Pro Ala
65                  70                  75                  80

Val Glu Leu Ala Ile Glu Gln Ile Arg Asn Glu Ser Leu Leu Arg Pro
                85                  90                  95

Tyr Phe Leu Asp Leu Arg Leu Tyr Asp Thr Glu Cys Asp Asn Ala Lys
            100                 105                 110

Gly Leu Lys Ala Phe Tyr Asp Ala Ile Lys Tyr Gly Pro Asn His Leu
        115                 120                 125

Met Val Phe Gly Gly Val Cys Pro Ser Val Thr Ser Ile Ile Ala Glu
    130                 135                 140

Ser Leu Gln Gly Trp Asn Leu Val Gln Leu Ser Phe Ala Ala Thr Thr
145                 150                 155                 160

Pro Val Leu Ala Asp Lys Lys Lys Tyr Pro Tyr Phe Phe Arg Thr Val
                165                 170                 175

Pro Ser Asp Asn Ala Val Asn Pro Ala Ile Leu Lys Leu Leu Lys His
            180                 185                 190

Tyr Gln Trp Lys Arg Val Gly Thr Leu Thr Gln Asp Val Gln Arg Phe
        195                 200                 205

Ser Glu Val Arg Asn Asp Leu Thr Gly Val Leu Tyr Gly Glu Asp Ile
    210                 215                 220

Glu Ile Ser Asp Thr Glu Ser Phe Ser Asn Asp Pro Cys Thr Ser Val
225                 230                 235                 240

Lys Lys Leu Lys Gly Asn Asp Val Arg Ile Ile Leu Gly Gln Phe Asp
                245                 250                 255

Gln Asn Met Ala Ala Lys Val Phe Cys Cys Ala Tyr Glu Glu Asn Met
            260                 265                 270

Tyr Gly Ser Lys Tyr Gln Trp Ile Ile Pro Gly Trp Tyr Glu Pro Ser
        275                 280                 285

Trp Trp Glu Gln Val His Thr Glu Ala Asn Ser Ser Arg Cys Leu Arg
    290                 295                 300

Lys Asn Leu Leu Ala Ala Met Glu Gly Tyr Ile Gly Val Asp Phe Glu
305                 310                 315                 320

Pro Leu Ser Ser Lys Gln Ile Lys Thr Ile Ser Gly Lys Thr Pro Gln
                325                 330                 335

Gln Tyr Glu Arg Glu Tyr Asn Asn Lys Arg Ser Gly Val Gly Pro Ser
            340                 345                 350

Lys Phe His Gly Tyr Ala Tyr Asp Gly Ile Trp Val Ile Ala Lys Thr
        355                 360                 365
```

```
Leu Gln Arg Ala Met Glu Thr Leu His Ala Ser Ser Arg His Gln Arg
    370                 375                 380

Ile Gln Asp Phe Asn Tyr Thr Asp His Thr Leu Gly Arg Ile Ile Leu
385                 390                 395                 400

Asn Ala Met Asn Glu Thr Asn Phe Phe Gly Val Thr Gly Gln Val Val
                405                 410                 415

Phe Arg Asn Gly Glu Arg Met Gly Thr Ile Lys Phe Thr Gln Phe Gln
            420                 425                 430

Asp Ser Arg Glu Val Lys Val Gly Glu Tyr Asn Ala Val Ala Asp Thr
        435                 440                 445

Leu Glu Ile Ile Asn Asp Thr Ile Arg Phe Gln Gly Ser Glu Pro Pro
    450                 455                 460

Lys Asp Lys Thr Ile Ile Leu Glu Gln Leu Arg Lys Ile Ser Leu Pro
465                 470                 475                 480

Leu Tyr Ser Ile Leu Ser Ala Leu Thr Ile Leu Gly Met Ile Met Ala
                485                 490                 495

Ser Ala Phe Leu Phe Phe Asn Ile Lys Asn Arg Asn Gln Lys Leu Ile
            500                 505                 510

Lys Met Ser Ser Pro Tyr Met Asn Asn Leu Ile Ile Leu Gly Gly Met
        515                 520                 525

Leu Ser Tyr Ala Ser Ile Phe Leu Phe Gly Leu Asp Gly Ser Phe Val
    530                 535                 540

Ser Glu Lys Thr Phe Glu Thr Leu Cys Thr Val Arg Thr Trp Ile Leu
545                 550                 555                 560

Thr Val Gly Tyr Thr Thr Ala Phe Gly Ala Met Phe Ala Lys Thr Trp
                565                 570                 575

Arg Val His Ala Ile Phe Lys Asn Val Lys Met Lys Lys Lys Ile Ile
            580                 585                 590

Lys Asp Gln Lys Leu Leu Val Ile Val Gly Gly Met Leu Leu Ile Asp
        595                 600                 605

Leu Cys Ile Leu Ile Cys Trp Gln Ala Val Asp Pro Leu Arg Arg Thr
    610                 615                 620

Val Glu Lys Tyr Ser Met Glu Pro Asp Pro Ala Gly Arg Asp Ile Ser
625                 630                 635                 640

Ile Arg Pro Leu Leu Glu His Cys Glu Asn Thr His Met Thr Ile Trp
                645                 650                 655

Leu Gly Ile Val Tyr Ala Tyr Lys Gly Leu Leu Met Leu Phe Gly Cys
            660                 665                 670
```

Phe Leu Ala Trp Glu Thr Arg Asn Val Ser Ile Pro Ala Leu Asn Asp
675 680 685

Ser Lys Tyr Ile Gly Met Ser Val Tyr Asn Val Gly Ile Met Cys Ile
690 695 700

Ile Gly Ala Ala Val Ser Phe Leu Thr Arg Asp Gln Pro Asn Val Gln
705 710 715 720

Phe Cys Ile Val Ala Leu Val Ile Ile Phe Cys Ser Thr Ile Thr Leu
725 730 735

Cys Leu Val Phe Val Pro Lys Leu Ile Thr Leu Arg Thr Asn Pro Asp
740 745 750

Ala Ala Thr Gln Asn Arg Arg Phe Gln Phe Thr Gln Asn Gln Lys Lys
755 760 765

Glu Asp Ser Lys Thr Ser Thr Ser Val Thr Ser Val Asn Gln Ala Ser
770 775 780

Thr Ser Arg Leu Glu Gly Leu Gln Ser Glu Asn His Arg Leu Arg Met
785 790 795 800

Lys Ile Thr Glu Leu Asp Lys Asp Leu Glu Glu Val Thr Met Gln Leu
805 810 815

Gln Asp Thr Pro Glu Lys Thr Thr Tyr Ile Lys Gln Asn His Tyr Gln
820 825 830

Glu Leu Asn Asp Ile Leu Asn Leu Gly Asn Phe Thr Glu Ser Thr Asp
835 840 845

Gly Gly Lys Ala Ile Leu Lys Asn His Leu Asp Gln Asn Pro Gln Leu
850 855 860

Gln Trp Asn Thr Thr Glu Pro Ser Arg Thr Cys Lys Asp Pro Ile Glu
865 870 875 880

Asp Ile Asn Ser Pro Glu His Ile Gln Arg Arg Leu Ser Leu Gln Leu
885 890 895

Pro Ile Leu His His Ala Tyr Leu Pro Ser Ile Gly Gly Val Asp Ala
900 905 910

Ser Cys Val Ser Pro Cys Val Ser Pro Thr Ala Ser Pro Arg His Arg
915 920 925

His Val Pro Pro Ser Phe Arg Val Met Val Ser Gly Leu Ser Asp
930 935 940

<210> 5
<211> 960
<212> PRT
<213> Rat

<400> 5

Met Leu Leu Leu Leu Leu Val Pro Leu Phe Leu Arg Pro Leu Gly Ala
1   5   10   15

Gly Gly Ala Gln Thr Pro Asn Ala Thr Ser Glu Gly Cys Gln Ile Ile
            20   25   30

His Pro Pro Trp Glu Gly Gly Ile Arg Tyr Arg Gly Leu Thr Arg Asp
        35   40   45

Gln Val Lys Ala Ile Asn Phe Leu Pro Val Asp Tyr Glu Ile Glu Tyr
    50   55   60

Val Cys Arg Gly Glu Arg Glu Val Val Gly Pro Lys Val Arg Lys Cys
65   70   75   80

Leu Ala Asn Gly Ser Trp Thr Asp Met Asp Thr Pro Ser Arg Cys Val
                85   90   95

Arg Ile Cys Ser Lys Ser Tyr Leu Thr Leu Glu Asn Gly Lys Val Phe
            100   105   110

Leu Thr Gly Gly Asp Leu Pro Ala Leu Asp Gly Ala Arg Val Glu Phe
        115   120   125

Arg Cys Asp Pro Asp Phe His Leu Val Gly Ser Ser Arg Ser Val Cys
    130   135   140

Ser Gln Gly Gln Trp Ser Thr Pro Lys Pro His Cys Gln Val Asn Arg
145   150   155   160

Thr Pro His Ser Glu Arg Arg Ala Val Tyr Ile Gly Ala Leu Phe Pro
                165   170   175

Met Ser Gly Gly Trp Pro Gly Gly Gln Ala Cys Gln Pro Ala Val Glu
            180   185   190

Met Ala Leu Glu Asp Val Asn Ser Arg Arg Asp Ile Leu Pro Asp Tyr
        195   200   205

Glu Leu Lys Leu Ile His His Asp Ser Lys Cys Asp Pro Gly Gln Ala
    210   215   220

Thr Lys Tyr Leu Tyr Glu Leu Leu Tyr Asn Asp Pro Ile Lys Ile Ile
225   230   235   240

Leu Met Pro Gly Cys Ser Ser Val Ser Thr Leu Val Ala Glu Ala Ala
                245   250   255

Arg Met Trp Asn Leu Ile Val Leu Ser Tyr Gly Ser Ser Ser Pro Ala
            260   265   270

Leu Ser Asn Arg Gln Arg Phe Pro Thr Phe Phe Arg Thr His Pro Ser
        275   280   285

Ala Thr Leu His Asn Pro Thr Arg Val Lys Leu Phe Glu Lys Trp Gly
    290   295   300

```
Trp Lys Lys Ile Ala Thr Ile Gln Gln Thr Thr Glu Val Phe Thr Ser
305                 310                 315                 320

Thr Leu Asp Asp Leu Glu Glu Arg Val Lys Glu Ala Gly Ile Glu Ile
                325                 330                 335

Thr Phe Arg Gln Ser Phe Phe Ser Asp Pro Ala Val Pro Val Lys Asn
            340                 345                 350

Leu Lys Arg Gln Asp Ala Arg Ile Ile Val Gly Leu Phe Tyr Glu Thr
        355                 360                 365

Glu Ala Arg Lys Val Phe Cys Glu Val Tyr Lys Glu Arg Leu Phe Gly
    370                 375                 380

Lys Lys Tyr Val Trp Phe Leu Ile Gly Trp Tyr Ala Asp Asn Trp Phe
385                 390                 395                 400

Lys Thr Tyr Asp Pro Ser Ile Asn Cys Thr Val Glu Glu Met Thr Glu
                405                 410                 415

Ala Val Glu Gly His Ile Thr Thr Glu Ile Val Met Leu Asn Pro Ala
            420                 425                 430

Asn Thr Arg Ser Ile Ser Asn Met Thr Ser Gln Glu Phe Val Glu Lys
        435                 440                 445

Leu Thr Lys Arg Leu Lys Arg His Pro Glu Glu Thr Gly Gly Phe Gln
    450                 455                 460

Glu Ala Pro Leu Ala Tyr Asp Ala Ile Trp Ala Leu Ala Leu Ala Leu
465                 470                 475                 480

Asn Lys Thr Ser Gly Gly Gly Gly Arg Ser Gly Val Arg Leu Glu Asp
                485                 490                 495

Phe Asn Tyr Asn Asn Gln Thr Ile Thr Asp Gln Ile Tyr Arg Ala Met
            500                 505                 510

Asn Ser Ser Ser Phe Glu Gly Val Ser Gly His Val Val Phe Asp Ala
        515                 520                 525

Ser Gly Ser Arg Met Ala Trp Thr Leu Ile Glu Gln Leu Gln Gly Gly
    530                 535                 540

Ser Tyr Lys Lys Ile Gly Tyr Tyr Asp Ser Thr Lys Asp Asp Leu Ser
545                 550                 555                 560

Trp Ser Lys Thr Asp Lys Trp Ile Gly Gly Ser Pro Pro Ala Asp Gln
                565                 570                 575

Ile Leu Val Ile Lys Thr Phe Arg Phe Leu Ser Gln Lys Leu Phe Ile
            580                 585                 590

Ser Val Ser Val Leu Ser Ser Leu Gly Ile Val Leu Ala Val Val Cys
        595                 600                 605
```

```
Leu Ser Phe Asn Ile Tyr Asn Ser His Val Arg Tyr Ile Gln Asn Ser
    610                 615                 620

Gln Pro Asn Leu Asn Asn Leu Thr Ala Val Gly Cys Ser Leu Ala Leu
625                 630                 635                 640

Ala Ala Val Phe Pro Leu Gly Leu Asp Gly Tyr His Ile Gly Arg Ser
                645                 650                 655

Gln Phe Pro Phe Val Cys Gln Ala Arg Leu Trp Leu Leu Gly Leu Gly
            660                 665                 670

Phe Ser Leu Gly Tyr Gly Ser Met Phe Thr Lys Ile Trp Trp Val His
        675                 680                 685

Thr Val Phe Thr Lys Lys Glu Glu Lys Lys Glu Trp Arg Lys Thr Leu
    690                 695                 700

Glu Pro Trp Lys Leu Tyr Ala Thr Val Gly Leu Leu Val Gly Met Asp
705                 710                 715                 720

Val Leu Thr Leu Ala Ile Trp Gln Ile Val Asp Pro Leu His Arg Thr
                725                 730                 735

Ile Glu Thr Phe Ala Lys Glu Glu Pro Lys Glu Asp Ile Asp Val Ser
            740                 745                 750

Ile Leu Pro Gln Leu Glu His Cys Ser Ser Lys Lys Met Asn Thr Trp
        755                 760                 765

Leu Gly Ile Phe Tyr Gly Tyr Lys Gly Leu Leu Leu Leu Leu Gly Ile
    770                 775                 780

Phe Leu Ala Tyr Glu Thr Lys Ser Val Ser Thr Glu Lys Ile Asn Asp
785                 790                 795                 800

His Arg Ala Val Gly Met Ala Ile Tyr Asn Val Ala Val Leu Cys Leu
                805                 810                 815

Ile Thr Ala Pro Val Thr Met Ile Leu Ser Ser Gln Gln Asp Ala Ala
            820                 825                 830

Phe Ala Phe Ala Ser Leu Ala Ile Val Phe Ser Ser Tyr Ile Thr Leu
        835                 840                 845

Val Val Leu Phe Val Pro Lys Met Arg Arg Leu Ile Thr Arg Gly Glu
    850                 855                 860

Trp Gln Ser Glu Thr Gln Asp Thr Met Lys Thr Gly Ser Ser Thr Asn
865                 870                 875                 880

Asn Asn Glu Glu Glu Lys Ser Arg Leu Leu Glu Lys Glu Asn Arg Glu
                885                 890                 895

Leu Glu Lys Ile Ile Ala Glu Lys Glu Glu Arg Val Ser Glu Leu Arg
            900                 905                 910
```

His Gln Leu Gln Ser Arg Gln Gln Leu Arg Ser Arg Arg His Pro Pro
915 920 925

Thr Pro Pro Asp Pro Ser Gly Gly Leu Pro Arg Gly Pro Ser Glu Pro
930 935 940

Pro Asp Arg Leu Ser Cys Asp Gly Ser Arg Val His Leu Leu Tyr Lys
945 950 955 960

<210> 6
<211> 844
<212> PRT
<213> Rat

<400> 6

Met Gly Pro Gly Gly Pro Cys Thr Pro Val Gly Trp Pro Leu Pro Leu
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Leu Leu Val Met Ala Ala Gly Val Ala Pro Val Trp Ala Ser His Ser
20 25 30

Pro His Leu Pro Arg Pro His Pro Arg Val Pro Pro His Pro Ser Ser
35 40 45

Glu Arg Arg Ala Val Tyr Ile Gly Ala Leu Phe Pro Met Ser Gly Gly
50 55 60

Trp Pro Gly Gly Gln Ala Cys Gln Pro Ala Val Glu Met Ala Leu Glu
65 70 75 80

Asp Val Asn Ser Arg Arg Asp Ile Leu Pro Asp Tyr Glu Leu Lys Leu
85 90 95

Ile His His Asp Ser Lys Cys Asp Pro Gly Gln Ala Thr Lys Tyr Leu
100 105 110

Tyr Glu Leu Leu Tyr Asn Asp Pro Ile Lys Ile Ile Leu Met Pro Gly
115 120 125

Cys Ser Ser Val Ser Thr Leu Val Ala Glu Ala Ala Arg Met Trp Asn
130 135 140

Leu Ile Val Leu Ser Tyr Gly Ser Ser Ser Pro Ala Leu Ser Asn Arg
145 150 155 160

Gln Arg Phe Pro Thr Phe Phe Arg Thr His Pro Ser Ala Thr Leu His
165 170 175

Asn Pro Thr Arg Val Lys Leu Phe Glu Lys Trp Gly Trp Lys Lys Ile
180 185 190

Ala Thr Ile Gln Gln Thr Thr Glu Val Phe Thr Ser Thr Leu Asp Asp
195 200 205

Leu Glu Glu Arg Val Lys Glu Ala Gly Ile Glu Ile Thr Phe Arg Gln
    210   215   220

Ser Phe Phe Ser Asp Pro Ala Val Pro Val Lys Asn Leu Lys Arg Gln
225   230   235   240

Asp Ala Arg Ile Ile Val Gly Leu Phe Tyr Glu Thr Glu Ala Arg Lys
                245   250   255

Val Phe Cys Glu Val Tyr Lys Glu Arg Leu Phe Gly Lys Lys Tyr Val
            260   265   270

Trp Phe Leu Ile Gly Trp Tyr Ala Asp Asn Trp Phe Lys Thr Tyr Asp
        275   280   285

Pro Ser Ile Asn Cys Thr Val Glu Glu Met Thr Glu Ala Val Glu Gly
    290   295   300

His Ile Thr Thr Glu Ile Val Met Leu Asn Pro Ala Asn Thr Arg Ser
305   310   315   320

Ile Ser Asn Met Thr Ser Gln Glu Phe Val Glu Lys Leu Thr Lys Arg
                325   330   335

Leu Lys Arg His Pro Glu Glu Thr Gly Gly Phe Gln Glu Ala Pro Leu
            340   345   350

Ala Tyr Asp Ala Ile Trp Ala Leu Ala Leu Ala Leu Asn Lys Thr Ser
        355   360   365

Gly Gly Gly Gly Arg Ser Gly Val Arg Leu Glu Asp Phe Asn Tyr Asn
    370   375   380

Asn Gln Thr Ile Thr Asp Gln Ile Tyr Arg Ala Met Asn Ser Ser Ser
385   390   395   400

Phe Glu Gly Val Ser Gly His Val Val Phe Asp Ala Ser Gly Ser Arg
                405   410   415

Met Ala Trp Thr Leu Ile Glu Gln Leu Gln Gly Gly Ser Tyr Lys Lys
            420   425   430

Ile Gly Tyr Tyr Asp Ser Thr Lys Asp Asp Leu Ser Trp Ser Lys Thr
        435   440   445

Asp Lys Trp Ile Gly Gly Ser Pro Pro Ala Asp Gln Ile Leu Val Ile
    450   455   460

Lys Thr Phe Arg Phe Leu Ser Gln Lys Leu Phe Ile Ser Val Ser Val
465   470   475   480

Leu Ser Ser Leu Gly Ile Val Leu Ala Val Val Cys Leu Ser Phe Asn
                485   490   495

Ile Tyr Asn Ser His Val Arg Tyr Ile Gln Asn Ser Gln Pro Asn Leu
            500   505   510

Asn Asn Leu Thr Ala Val Gly Cys Ser Leu Ala Leu Ala Ala Val Phe
515 520 525

Pro Leu Gly Leu Asp Gly Tyr His Ile Gly Arg Ser Gln Phe Pro Phe
530 535 540

Val Cys Gln Ala Arg Leu Trp Leu Leu Gly Leu Gly Phe Ser Leu Gly
545 550 555 560

Tyr Gly Ser Met Phe Thr Lys Ile Trp Trp Val His Thr Val Phe Thr
565 570 575

Lys Lys Glu Glu Lys Lys Glu Trp Arg Lys Thr Leu Glu Pro Trp Lys
580 585 590

Leu Tyr Ala Thr Val Gly Leu Leu Val Gly Met Asp Val Leu Thr Leu
595 600 605

Ala Ile Trp Gln Ile Val Asp Pro Leu His Arg Thr Ile Glu Thr Phe
610 615 620

Ala Lys Glu Glu Pro Lys Glu Asp Ile Asp Val Ser Ile Leu Pro Gln
625 630 635 640

Leu Glu His Cys Ser Ser Lys Lys Met Asn Thr Trp Leu Gly Ile Phe
645 650 655

Tyr Gly Tyr Lys Gly Leu Leu Leu Leu Leu Gly Ile Phe Leu Ala Tyr
660 665 670

Glu Thr Lys Ser Val Ser Thr Glu Lys Ile Asn Asp His Arg Ala Val
675 680 685

Gly Met Ala Ile Tyr Asn Val Ala Val Leu Cys Leu Ile Thr Ala Pro
690 695 700

Val Thr Met Ile Leu Ser Ser Gln Gln Asp Ala Ala Phe Ala Phe Ala
705 710 715 720

Ser Leu Ala Ile Val Phe Ser Ser Tyr Ile Thr Leu Val Val Leu Phe
725 730 735

Val Pro Lys Met Arg Arg Leu Ile Thr Arg Gly Glu Trp Gln Ser Glu
740 745 750

Thr Gln Asp Thr Met Lys Thr Gly Ser Ser Thr Asn Asn Asn Glu Glu
755 760 765

Glu Lys Ser Arg Leu Leu Glu Lys Glu Asn Arg Glu Leu Glu Lys Ile
770 775 780

Ile Ala Glu Lys Glu Glu Arg Val Ser Glu Leu Arg His Gln Leu Gln
785 790 795 800

Ser Arg Gln Gln Leu Arg Ser Arg Arg His Pro Pro Thr Pro Pro Asp
805 810 815

Pro Ser Gly Gly Leu Pro Arg Gly Pro Ser Glu Pro Pro Asp Arg Leu
820 825 830

Ser Cys Asp Gly Ser Arg Val His Leu Leu Tyr Lys
835 840

<210> 7
<211> 961
<212> PRT
<213> Human

<400> 7

Met Leu Leu Leu Leu Leu Leu Ala Pro Leu Phe Leu Arg Pro Pro Gly
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Ala Gly Gly Ala Gln Thr Pro Asn Ala Thr Ser Glu Gly Cys Gln Ile
20 25 30

Ile His Pro Pro Trp Glu Gly Gly Ile Arg Tyr Arg Gly Leu Thr Arg
35 40 45

Asp Gln Val Lys Ala Ile Asn Phe Leu Pro Val Asp Tyr Glu Ile Glu
50 55 60

Tyr Val Cys Arg Gly Glu Arg Glu Val Val Gly Pro Lys Val Arg Lys
65 70 75 80

Cys Leu Ala Asn Gly Ser Trp Thr Asp Met Asp Thr Pro Ser Arg Cys
85 90 95

Val Arg Ile Cys Ser Lys Ser Tyr Leu Thr Leu Glu Asn Gly Lys Val
100 105 110

Phe Leu Thr Gly Gly Asp Leu Pro Ala Leu Asp Gly Ala Arg Val Asp
115 120 125

Phe Arg Cys Asp Pro Asp Phe His Leu Val Gly Ser Ser Arg Ser Ile
130 135 140

Cys Ser Gln Gly Gln Trp Ser Thr Pro Lys Pro His Cys Gln Val Asn
145 150 155 160

Arg Thr Pro His Ser Glu Arg Arg Ala Val Tyr Ile Gly Ala Leu Phe
165 170 175

Pro Met Ser Gly Gly Trp Pro Gly Gly Gln Ala Cys Gln Pro Ala Val
180 185 190

Glu Met Ala Leu Glu Asp Val Asn Ser Arg Arg Asp Ile Leu Pro Asp
195 200 205

Tyr Glu Leu Lys Leu Ile His His Asp Ser Lys Cys Asp Pro Gly Gln
210 215 220

Ala Thr Lys Tyr Leu Tyr Glu Leu Leu Tyr Asn Asp Pro Ile Lys Ile
225 230 235 240

Ile Leu Met Pro Gly Cys Ser Ser Val Ser Thr Leu Val Ala Glu Ala
245 250 255

Ala Arg Met Trp Asn Leu Ile Val Leu Ser Tyr Gly Ser Ser Ser Pro
260 265 270

Ala Leu Ser Asn Arg Gln Arg Phe Pro Thr Phe Phe Arg Thr His Pro
275 280 285

Ser Ala Thr Leu His Asn Pro Thr Arg Val Lys Leu Phe Glu Lys Trp
290 295 300

Gly Trp Lys Lys Ile Ala Thr Ile Gln Gln Thr Thr Glu Val Phe Thr
305 310 315 320

Ser Thr Leu Asp Asp Leu Glu Glu Arg Val Lys Glu Ala Gly Ile Glu
325 330 335

Ile Thr Phe Arg Gln Ser Phe Phe Ser Asp Pro Ala Val Pro Val Lys
340 345 350

Asn Leu Lys Arg Gln Asp Ala Arg Ile Ile Val Gly Leu Phe Tyr Glu
355 360 365

Thr Glu Ala Arg Lys Val Phe Cys Glu Val Tyr Lys Glu Arg Leu Phe
370 375 380

Gly Lys Lys Tyr Val Trp Phe Leu Ile Gly Trp Tyr Ala Asp Asn Trp
385 390 395 400

Phe Lys Ile Tyr Asp Pro Ser Ile Asn Cys Thr Val Asp Glu Met Thr
405 410 415

Glu Ala Val Glu Gly His Ile Thr Thr Glu Ile Val Met Leu Asn Pro
420 425 430

Ala Asn Thr Arg Ser Ile Ser Asn Met Thr Ser Gln Glu Phe Val Glu
435 440 445

Lys Leu Thr Lys Arg Leu Lys Arg His Pro Glu Glu Thr Gly Gly Phe
450 455 460

Gln Glu Ala Pro Leu Ala Tyr Asp Ala Ile Trp Ala Leu Ala Leu Ala
465 470 475 480

Leu Asn Lys Thr Ser Gly Gly Gly Gly Arg Ser Gly Val Arg Leu Glu
485 490 495

Asp Phe Asn Tyr Asn Asn Gln Thr Ile Thr Asp Gln Ile Tyr Arg Ala
500 505 510

Met Asn Ser Ser Ser Phe Glu Gly Val Ser Gly His Val Val Phe Asp
515 520 525

```
Ala Ser Gly Ser Arg Met Ala Trp Thr Leu Ile Glu Gln Leu Gln Gly
    530                 535                 540

Gly Ser Tyr Lys Lys Ile Gly Tyr Tyr Asp Ser Thr Lys Asp Asp Leu
545                 550                 555                 560

Ser Trp Ser Lys Thr Asp Lys Trp Ile Gly Gly Ser Pro Pro Ala Asp
                565                 570                 575

Gln Thr Leu Val Ile Lys Thr Phe Arg Phe Leu Ser Gln Lys Leu Phe
            580                 585                 590

Ile Ser Val Ser Val Leu Ser Ser Leu Gly Ile Val Leu Ala Val Val
        595                 600                 605

Cys Leu Ser Phe Asn Ile Tyr Asn Ser His Val Arg Tyr Ile Gln Asn
    610                 615                 620

Ser Gln Pro Asn Leu Asn Asn Leu Thr Ala Val Gly Cys Ser Leu Ala
625                 630                 635                 640

Leu Ala Ala Val Phe Pro Leu Gly Leu Asp Gly Tyr His Ile Gly Arg
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Asn Gln Phe Pro Phe Val Cys Gln Ala Arg Leu Trp Leu Leu Gly Leu
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Gly Phe Ser Leu Gly Tyr Gly Ser Met Phe Thr Lys Ile Trp Trp Val
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His Thr Val Phe Thr Lys Lys Glu Glu Lys Lys Glu Trp Arg Lys Thr
    690                 695                 700

Leu Glu Pro Trp Lys Leu Tyr Ala Thr Val Gly Leu Leu Val Gly Met
705                 710                 715                 720

Asp Val Leu Thr Leu Ala Ile Trp Gln Ile Val Asp Pro Leu His Arg
                725                 730                 735

Thr Ile Glu Thr Phe Ala Lys Glu Glu Pro Lys Glu Asp Ile Asp Val
            740                 745                 750

Ser Ile Leu Pro Gln Leu Glu His Cys Ser Ser Arg Lys Met Asn Thr
        755                 760                 765

Trp Leu Gly Ile Phe Tyr Gly Tyr Lys Gly Leu Leu Leu Leu Leu Gly
    770                 775                 780

Ile Phe Leu Ala Tyr Glu Thr Lys Ser Val Ser Thr Glu Lys Ile Asn
785                 790                 795                 800

Asp His Arg Ala Val Gly Met Ala Ile Tyr Asn Val Ala Val Leu Cys
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            820                 825                 830
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Arg His Gln Leu Gln Ser Arg Gln Gln Leu Arg Ser Arg Arg His Pro
915 920 925

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Glu Arg Arg Ala Val Tyr Ile Gly Ala Leu Phe Pro Met Ser Gly Gly
50 55 60

Trp Pro Gly Gly Gln Ala Cys Gln Pro Ala Val Glu Met Ala Leu Glu
65 70 75 80

Asp Val Asn Ser Arg Arg Asp Ile Leu Pro Asp Tyr Glu Leu Lys Leu
85 90 95

Ile His His Asp Ser Lys Cys Asp Pro Gly Gln Ala Thr Lys Tyr Leu
100 105 110

Tyr Glu Leu Leu Tyr Asn Asp Pro Ile Lys Ile Ile Leu Met Pro Gly
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Cys Ser Ser Val Ser Thr Leu Val Ala Glu Ala Ala Arg Met Trp Asn
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Gln Arg Phe Pro Thr Phe Phe Arg Thr His Pro Ser Ala Thr Leu His
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Asn Pro Thr Arg Val Lys Leu Phe Glu Lys Trp Gly Trp Lys Lys Ile
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245 250 255

Val Phe Cys Glu Val Tyr Lys Glu Arg Leu Phe Gly Lys Lys Tyr Val
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Pro Ser Ile Asn Cys Thr Val Asp Glu Met Thr Glu Ala Val Glu Gly
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His Ile Thr Thr Glu Ile Val Met Leu Asn Pro Ala Asn Thr Arg Ser
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Ile Ser Asn Met Thr Ser Gln Glu Phe Val Glu Lys Leu Thr Lys Arg
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Leu Lys Arg His Pro Glu Glu Thr Gly Gly Phe Gln Glu Ala Pro Leu
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Ala Tyr Asp Ala Ile Trp Ala Leu Ala Leu Ala Leu Asn Lys Thr Ser
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420 425 430

Ile Gly Tyr Tyr Asp Ser Thr Lys Asp Asp Leu Ser Trp Ser Lys Thr
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Lys Thr Phe Arg Phe Leu Ser Gln Lys Leu Phe Ile Ser Val Ser Val
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Ile Tyr Asn Ser His Val Arg Tyr Ile Gln Asn Ser Gln Pro Asn Leu
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Asn Asn Leu Thr Ala Val Gly Cys Ser Leu Ala Leu Ala Ala Val Phe
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Ala Lys Glu Glu Pro Lys Glu Asp Ile Asp Val Ser Ile Leu Pro Gln
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Leu Glu His Cys Ser Ser Arg Lys Met Asn Thr Trp Leu Gly Ile Phe
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660 665 670

Glu Thr Lys Ser Val Ser Thr Glu Lys Ile Asn Asp His Arg Ala Val
675 680 685

Gly Met Ala Ile Tyr Asn Val Ala Val Leu Cys Leu Ile Thr Ala Pro
690 695 700

Val Thr Met Ile Leu Ser Ser Gln Gln Asp Ala Ala Phe Ala Phe Ala
705 710 715 720

Ser Leu Ala Ile Val Phe Ser Ser Tyr Ile Thr Leu Val Val Leu Phe
725 730 735

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Ala Gln Asp Thr Met Lys Thr Gly Ser Ser Thr Asn Asn Asn Glu Glu
        755                 760                 765

Glu Lys Ser Arg Leu Leu Glu Lys Glu Asn Arg Glu Leu Glu Lys Ile
    770                 775                 780

Ile Ala Glu Lys Glu Glu Arg Val Ser Glu Leu Arg His Gln Leu Gln
785                 790                 795                 800

Ser Arg Gln Gln Leu Arg Ser Arg Arg His Pro Pro Thr Pro Pro Glu
                805                 810                 815

Pro Ser Gly Gly Leu Pro Arg Gly Pro Pro Glu Pro Pro Asp Arg Leu
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acc tct gcc tac ggg cca gac cag cga gcc caa aag aag ggg gac att       96
Thr Ser Ala Tyr Gly Pro Asp Gln Arg Ala Gln Lys Lys Gly Asp Ile
            20                  25                  30

atc ctt ggg ggg ctc ttt cct att cat ttt gga gta gca gct aaa gat      144
Ile Leu Gly Gly Leu Phe Pro Ile His Phe Gly Val Ala Ala Lys Asp
        35                  40                  45

caa gat ctc aaa tca agg ccg gag tct gtg gaa tgt atc agg tat aat      192
Gln Asp Leu Lys Ser Arg Pro Glu Ser Val Glu Cys Ile Arg Tyr Asn
    50                  55                  60

ttc cgt ggg ttt cgc tgg tta cag gct atg ata ttt gcc ata gag gag      240
Phe Arg Gly Phe Arg Trp Leu Gln Ala Met Ile Phe Ala Ile Glu Glu
65                  70                  75                  80

ata aac agc agc cca gcc ctt ctt ccc aac ttg acg ctg gga tac agg      288
Ile Asn Ser Ser Pro Ala Leu Leu Pro Asn Leu Thr Leu Gly Tyr Arg
                85                  90                  95
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ata ttt gac act tgc aac acc gtt tct aag gcc ttg gaa gcc acc ctg      336
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agt ttt gtt gct caa aac aaa att gat tct ttg aac ctt gat gag ttc      384
Ser Phe Val Ala Gln Asn Lys Ile Asp Ser Leu Asn Leu Asp Glu Phe
        115                 120                 125

tgc aac tgc tca gag cac att ccc tct acg att gct gtg gtg gga gca      432
Cys Asn Cys Ser Glu His Ile Pro Ser Thr Ile Ala Val Val Gly Ala
    130                 135                 140

act ggc tca ggc gtc tcc acg gca gtg gca aat ctg ctg ggg ctc ttc      480
Thr Gly Ser Gly Val Ser Thr Ala Val Ala Asn Leu Leu Gly Leu Phe
145                 150                 155                 160

tac att ccc cag gtc agt tat gcc tcc tcc agc aga ctc ctc agc aac      528
Tyr Ile Pro Gln Val Ser Tyr Ala Ser Ser Ser Arg Leu Leu Ser Asn
                165                 170                 175

aag aat caa ttc aag tct ttc ctc cga acc atc ccc aat gat gag cac      576
Lys Asn Gln Phe Lys Ser Phe Leu Arg Thr Ile Pro Asn Asp Glu His
            180                 185                 190

cag gcc act gcc atg gca gac atc atc gag tat ttc cgc tgg aac tgg      624
Gln Ala Thr Ala Met Ala Asp Ile Ile Glu Tyr Phe Arg Trp Asn Trp
        195                 200                 205

gtg ggc aca att gca gct gat gac gac tat ggg cgg ccg ggg att gag      672
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    210                 215                 220

aaa ttc cga gag gaa gct gag gaa agg gat atc tgc atc gac ttc agt      720
Lys Phe Arg Glu Glu Ala Glu Glu Arg Asp Ile Cys Ile Asp Phe Ser
225                 230                 235                 240

gaa ctc atc tcc cag tac tct gat gag gaa gag atc cag cat gtg gta      768
Glu Leu Ile Ser Gln Tyr Ser Asp Glu Glu Glu Ile Gln His Val Val
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gag gtg att caa aat tcc acg gcc aaa gtc atc gtg gtt ttc tcc agt      816
Glu Val Ile Gln Asn Ser Thr Ala Lys Val Ile Val Val Phe Ser Ser
            260                 265                 270

ggc cca gat ctt gag ccc ctc atc aag gag att gtc cgg cgc aat atc      864
Gly Pro Asp Leu Glu Pro Leu Ile Lys Glu Ile Val Arg Arg Asn Ile
        275                 280                 285

acg ggc aag atc tgg ctg gcc agc gag gcc tgg gcc agc tcc tcc ctg      912
Thr Gly Lys Ile Trp Leu Ala Ser Glu Ala Trp Ala Ser Ser Ser Leu
    290                 295                 300

atc gcc atg cct cag tac ttc cac gtg gtt ggc ggc acc att gga ttc      960
Ile Ala Met Pro Gln Tyr Phe His Val Val Gly Gly Thr Ile Gly Phe
305                 310                 315                 320
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gct ctg aag gct ggg cag atc cca ggc ttc cgg gaa ttc ctg aag aag      1008
Ala Leu Lys Ala Gly Gln Ile Pro Gly Phe Arg Glu Phe Leu Lys Lys
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gtc cat ccc agg aag tct gtc cac aat ggt ttt gcc aag gag ttt tgg      1056
Val His Pro Arg Lys Ser Val His Asn Gly Phe Ala Lys Glu Phe Trp
            340                 345                 350

gaa gaa aca ttt aac tgc cac ctc caa gaa ggt gca aaa gga cct tta      1104
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        355                 360                 365

cct gtg gac acc ttt ctg aga ggt cac gaa gaa agt ggc gac agg ttt      1152
Pro Val Asp Thr Phe Leu Arg Gly His Glu Glu Ser Gly Asp Arg Phe
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agc aac agc tcg aca gcc ttc cga ccc ctc tgt aca ggg gat gag aac      1200
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385                 390                 395                 400

atc agc agt gtc gag acc cct tac ata gat tac acg cat tta cgg ata      1248
Ile Ser Ser Val Glu Thr Pro Tyr Ile Asp Tyr Thr His Leu Arg Ile
                405                 410                 415

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gat ata tat acc tgc tta cct ggg aga ggg ctc ttc acc aat ggc tcc      1344
Asp Ile Tyr Thr Cys Leu Pro Gly Arg Gly Leu Phe Thr Asn Gly Ser
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tgt gca gac atc aag aaa gtt gag gcg tgg cag gtc ctg aag cac cta      1392
Cys Ala Asp Ile Lys Lys Val Glu Ala Trp Gln Val Leu Lys His Leu
    450                 455                 460

cgg cat cta aac ttt aca aac aat atg ggg gag cag gtg acc ttt gat      1440
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465                 470                 475                 480

gag tgt ggt gac ctg gtg ggg aac tat tcc atc atc aac tgg cac ctc      1488
Glu Cys Gly Asp Leu Val Gly Asn Tyr Ser Ile Ile Asn Trp His Leu
                485                 490                 495

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gtc tat gcc aag aag gga gaa aga ctc ttc atc aac gag gag aaa atc      1584
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        515                 520                 525

ctg tgg agt ggg ttc tcc agg gag gtg ccc ttc tcc aac tgc agc cga      1632
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aca gat gcc agt gcc tgt aac aag tgc cca gat gac ttc tgg tcc aat 1776
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gag aac cac acc tcc tgc att gcc aag gag atc gag ttt ctg tcg tgg 1824
Glu Asn His Thr Ser Cys Ile Ala Lys Glu Ile Glu Phe Leu Ser Trp
595 600 605

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tcc ctg ctc tgc tgc ttc tcc agc tcc ctg ttc ttc atc ggg gag ccc 2016
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cag gac tgg acg tgc cgc ctg cgc cag ccg gcc ttt ggc atc agc ttc 2064
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Val Leu Cys Ile Ser Cys Ile Leu Val Lys Thr Asn Arg Val Leu Leu
690 695 700

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gcc atc tgc ttc ttc ttt gcc ttc aag tcc cgg aag ctg ccg gag aac      2400
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785                 790                 795                 800

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Phe Asn Glu Ala Lys Phe Ile Thr Phe Ser Met Leu Ile Phe Phe Ile
                805                 810                 815

gtc tgg atc tcc ttc att cca gcc tat gcc agc acc tat ggc aag ttt      2496
Val Trp Ile Ser Phe Ile Pro Ala Tyr Ala Ser Thr Tyr Gly Lys Phe
            820                 825                 830

gtc tct gcc gta gag gtg att gcc atc ctg gca gcc agc ttt ggc ttg      2544
Val Ser Ala Val Glu Val Ile Ala Ile Leu Ala Ala Ser Phe Gly Leu
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ctg gcg tgc atc ttc ttc aac aag atc tac atc att ctc ttc aag cca      2592
Leu Ala Cys Ile Phe Phe Asn Lys Ile Tyr Ile Ile Leu Phe Lys Pro
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Phe Lys Val Ala Ala Arg Ala Thr Leu Arg Arg Ser Asn Val Ser Arg
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aag cgg tcc agc agc ctt gga ggc tcc acg gga tcc acc ccc tcc tcc      2736
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cag cag ccc ctg acc ctc cca cag cag caa cga tct cag cag cag ccc      2880
Gln Gln Pro Leu Thr Leu Pro Gln Gln Gln Arg Ser Gln Gln Gln Pro
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                965                 970                 975

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        995                 1000                1005

cga cac cag cca tta ctc ccg ctg cag tgc ggg gaa acg gac tta gat      3072
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ctg acc gtc cag gaa aca ggt ctg caa gga cct gtg ggt gga gac cag      3120
Leu Thr Val Gln Glu Thr Gly Leu Gln Gly Pro Val Gly Gly Asp Gln
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cgg cca gag gtg gag gac cct gaa gag ttg tcc cca gca ctt gta gtg      3168
Arg Pro Glu Val Glu Asp Pro Glu Glu Leu Ser Pro Ala Leu Val Val
                1045                1050                1055

tcc agt tca cag agc ttt gtc atc agt ggt gga ggc agc act gtt aca      3216
Ser Ser Ser Gln Ser Phe Val Ile Ser Gly Gly Gly Ser Thr Val Thr
            1060                1065                1070

gaa aac gta gtg aat tca                                              3234
Glu Asn Val Val Asn Ser
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(57) Abstract

The present invention features a novel $GABA_B$ receptor subtype ("$GABA_BR2$"). The cDNA sequence encoding $GABA_BR2$ is shown in Figures (1a–1n) as SEQ. ID. NO: 1. The $GABA_BR2$ amino acid sequence is provided in Figures (2a–2f) as SEQ. ID NO: 4.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/07352

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K14/47 C07K14/705 C12N15/12 C07K16/28 C12N5/06
A01K67/027

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 46675 A (NOVARTIS AG) 11 December 1997 (1997-12-11) cited in the application abstract page 6, paragraph 2 -page 7, paragraph 1 page 16, paragraph 2 -page 21, paragraph 2; examples 1-10	1-33
X	KAUPMANN K ET AL: "EXPRESSION CLONING OF GABAB RECEPTORS UNCOVERS SIMILARITY TO METABOTROPIC GLUTAMATE RECEPTORS" NATURE, vol. 386, no. 6622, 20 March 1997 (1997-03-20), pages 239-246, XP002032306 ISSN: 0028-0836 cited in the application the whole document	1-24, 26-29

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
23 September 1999	08/10/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Mateo Rosell, A.M.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	JONES, K.A. ET AL., : "GABAB receptors function as heteromeric assembly of the subunits GABABR1 and GABABR2" NATURE, vol. 396, 17 December 1998 (1998-12-17), pages 674-679, XP002116148 cited in the application page 677, right-hand column, paragraph 2 -page 678, left-hand column, paragraph 1; figures 1A,2	1-4, 15-17, 24,25, 28-32
P,X	WHITE J.H. ET AL., : "Heterodimerization is required for the formation of a functional GABAB receptor." NATURE, vol. 396, 17 December 1998 (1998-12-17), page 679-682 XP002116149 abstract; figures 1,4 page 681, left-hand column, last paragraph -page 682, right-hand column, paragraph 1	1-4, 15-17, 28-32
P,X	KAUPMANN K. ET AL., : "GABAB-receptor subtypes assemble into functional heteromeric complexes" NATURE, vol. 396, 17 December 1998 (1998-12-17), pages 683-687, XP002105268 abstract; figures 1,2	1-4, 15-17, 24,25, 28-32
P,X	DATABASE EMBL NUCLEOTIDE AND PROTEIN SEQUENCES,10 October 1998 (1998-10-10), XP002114719 HINXTON, GB AC= AF056085. Homo sapiens GABA-B receptor mRNA, complete cds. from nt 458 abstract	1-4, 15-17
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International Application No
PCT/US 99/07352

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
E	WO 99 20751 A (BOROWSKY BETH ;JONES KENNETH A (US); LAZ THOMAS M (US); SYNAPTIC P) 29 April 1999 (1999-04-29) fig 1a-e abstract page 6-19 page 91, line 1 -page 123, line 6 ---	1-24, 26-33
E	EP 0 937 777 A (SMITHKLINE BEECHAM PLC ;SMITHKLINE BEECHAM CORP (US)) 25 August 1999 (1999-08-25) see SEQ.ID.N.1 and 3. abstract page 3, line 10-25 page 6, line 44 -page 11, line 11 -----	1-24, 26-32

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/07352

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9746675 A	11-12-1997	AU 2028497 A	05-01-1998
		CA 2254862 A	11-12-1997
		EP 0907731 A	14-04-1999
WO 9920751 A	29-04-1999	AU 1101099 A	10-05-1999
EP 0937777 A	25-08-1999	WO 9942580 A	26-08-1999
		WO 9942603 A	26-08-1999

CORRECTED VERSION*

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(54) Title: GABA B RECEPTOR

(57) Abstract

The present invention features a novel $GABA_B$ receptor subtype ("$GABA_BR2$"). The cDNA sequence encoding $GABA_BR2$ is shown in Figures (1a–1n) as SEQ. ID. NO: 1. The $GABA_BR2$ amino acid sequence is provided in Figures (2a–2f) as SEQ. ID NO: 4.

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GABA$_B$ RECEPTOR

RELATED APPLICATIONS

The present application claims priority to Garrett *et al.* U.S. Serial No. 60/080,676, filed April 3, 1998, which is hereby incorporated by reference herein in its entirety including the drawings.

FIELD OF THE INVENTION

The present invention relates to a GABA$_B$ receptor, nucleic acid encoding a GABA$_B$ receptor, and uses of a GABA$_B$ receptor and nucleic acid encoding a GABA$_B$ receptor.

BACKGROUND

The references cited herein are not admitted to be prior art to the claimed invention.

GABA$_B$ receptors are metabotropic receptors coupled to guanine-nucleotide-binding proteins (G-proteins). GABA$_B$ receptors modulate synaptic transmission by inhibiting presynaptic transmitter release and by increasing K^+ conductance responsible for long-lasting inhibitory postsynaptic potentials. (Kaupmann *et al.*, *Nature 386*:239-246, 1997, hereby incorporated by reference herein.)

GABA$_B$ receptors are found in the mammalian brain, in locations outside of the brain, and in lower species. Outside of the brain, GABA$_B$ receptors have been identified on axon terminals and ganglion cell bodies of the autonomic nervous system, on fallopian tube and uterine intestinal smooth muscle cells, in the kidney cortex, urinary bladder muscle and on testicular interstitial cells. (*See,* Bowery, *Annu. Rev. Pharmacol. Toxicol. 33*:109-147, 1993, hereby incorporated by reference herein.)

GABA$_B$ receptors have been targeted to achieve therapeutic effects. Kerr and Ong, DDT 1:371-380, 1996, describe different compounds indicated to be GABA$_B$ receptor agonists and GABA$_B$ receptor antagonists. Kerr and Ong also review therapeutic implications of affecting GABA receptor activity including,

spasticity and motor control, analgesia, epilepsy, cognitive effects, psychiatric disorders, alcohol dependence and withdrawal, feeding behavior, cardiovascular and respiratory functions, and peripheral functions.

Bittiger *et al., Tips 4*:391-394, 1993, review therapeutic applications of $GABA_B$ receptor antagonists. Potential therapeutic applications noted by Bittiger *et al.* include cognitive processes, epilepsy, and depression.

Kaupmann *et al., Nature 386*:239-246, 1997, indicate that they cloned $GABA_B$ receptors. Two $GABA_B$ receptor proteins were indicated to be cloned from rat brain: $GABA_BR1a$ and $GABA_BR1b$. $GABA_BR1a$ differs from $GABA_BR1b$ in that the N-terminal 147 residues are replaced by 18 amino acids. $GABA_BR1a$ and $GABA_BR1b$ appear to be splice variants. The cloned $GABA_B$ receptors were indicated to negatively couple to adenylyl cyclases and show sequence similarity to the metabotropic receptors for L-glutamate(mGluR).

Kaupmann *et al., Nature 386*:239-246, 1997, indicate that bestfit sequence alignments with $GABA_B$ and different mGluR subtypes indicates 18-23% amino acid sequence identity and 43-48% related residues. (Devereux *et al., Nucleic Acids Res. 12*:387-395, 1984, was referenced for carrying out bestfit sequence alignments.) No significant sequence similarity was found with $GABA_A$ or $GABA_C$ receptors, or with other G-protein-coupled receptors which were not mGluR.

Kaupmann *et al.*, International Application Number PCT/EP97/01370, International Publication Number WO 97/46675, indicate that they have obtained rat $GABA_B$ clones, $GABA_BR1a$ and $GABA_BR1b$; and human $GABA_B$ clones, $GABA_BR1a/b$ (representing a partial receptor clone) and $GABA_BR1b$ (representing a full-length receptor clone). Amino acid sequence information, and encoding cDNA sequence information, is provided for the different human $GABA_B$ clones.

SUMMARY OF THE INVENTION

The present invention features a novel $GABA_B$ receptor subtype ("$GABA_BR2$"). The cDNA sequence encoding $GABA_BR2$ is shown in Figures 1a-1n as SEQ. ID. NO. 1. The $GABA_BR2$ amino acid sequence is provided in Figures 2a-2f as SEQ. ID. NO. 4.

Thus, a first aspect of the present invention describes a purified nucleic acid containing at least 18 contiguous nucleotides of SEQ. ID. NO. 1 which provides the nucleic acid encoding $GABA_BR2$. Preferably, the nucleic acid contains at least 27 contiguous nucleic acids, more preferably at least 45 contiguous nucleic acids, or most preferably the entire nucleic acid sequence provided in SEQ. ID. NO. 1. Advantages of longer-length nucleic acid include producing longer-length protein fragments having the sequence of $GABA_BR2$ which can be used, for example, to produce antibodies; and increased nucleic acid probe specificity under higher stringent hybridization assay conditions.

By "purified" in reference to nucleic acid is meant the nucleic acid is present in a form (*i.e.*, its association with other molecules) other than found in nature. For example, a purified receptor nucleic acid is separated from one or more nucleic acids which are present on the same chromosome. Preferably, the purified nucleic acid has been separated from at least 90% of the other nucleic acids present on the same chromosome. More preferably, the nucleic acid has been substantially purified such that it represents at least 75%, more preferably at least 85%, and most preferably at least 95% of the total nucleic acids present.

Another example of purified nucleic acid is recombinant nucleic acid. Preferably, recombinant nucleic acid contains nucleic acid encoding $GABA_BR2$ or $GABA_BR2$ fragments cloned in a vector. The vector contains the necessary elements for introducing heterologous nucleic acid into cells for either expression or replication.

Preferably, the vector is an expression vector containing elements needed for expressing a cloned nucleic acid sequence to produce a polypeptide. The expression vector contains a promoter region directing the initiation of RNA transcription, and DNA sequences which when transcribed into RNA signal protein synthesis initiation.

Recombinant nucleic acid may contain nucleic acid encoding for $GABA_BR2$, a $GABA_BR2$ fragment, or a $GABA_BR2$ derivative, under the control of genomic $GABA_BR2$ nucleic acid regulatory elements, or under the control of exogenous regulatory elements including

an exogenous promoter. By "exogenous" is meant a promoter that is not normally coupled *in vivo* transcriptionally to the coding sequence for $GABA_BR2$.

Another aspect of the present invention features a purified nucleic acid encoding at least 6 contiguous amino acids of the $GABA_BR2$ amino acid sequence which is provided as SEQ. ID. NO. 4. Due to the degeneracy of the genetic code, different combinations of nucleotides encode for the same polypeptide. Thus, numerous $GABA_BR2$ and $GABA_BR2$ fragments having the same amino acid sequences can be encoded for by different nucleic acid sequences. In preferred embodiments, the nucleic acid encodes at least 12, at least 18, at least 54 contiguous amino acids, or the entire amino acid sequence provided in SEQ. ID. NO. 4.

Another aspect of the present invention features a recombinant cell. The recombinant cell, which can be a tissue cell, is made up of a recombinant nucleic acid encoding $GABA_BR2$, a functional $GABA_BR2$ derivative, or a fragment thereof, and a cell able to express the nucleic acid. Recombinant cells have various uses including acting as biological factories to produce large amounts of polypeptides encoded for by the recombinant nucleic acid, as tools for screening for compounds which modulate $GABA_BR$ activity, and as research tools to study the effects of $GABA_BR$ activity.

Another aspect of the present invention features a purified nucleic acid comprising a nucleic acid sequence region substantially complementary to a sequence region of the SEQ. ID. NO. 1 or the perfect complement of SEQ. ID. NO. 1. Such nucleic acid can be used, for example, to specifically detect the presence of nucleic acid encoding for $GABA_BR2$ or a close relative thereof.

Substantially complementary nucleic acid regions contain at least 18 nucleotides in a stretch of 20 contiguous nucleotides which are complementary. Complementary nucleic acid form Watson-Crick A-T, G-C, and A-U, hydrogen bonds. More preferably, the nucleic acid comprises a nucleotide sequence of 20 contiguous nucleotides which has at least 19 bases, most preferably 20 bases, complementary to the nucleic acid sequence provided in SEQ. ID. NO. 1 or the perfect complement of SEQ. ID. NO. 1.

Another aspect of the present invention features a purified

polypeptide having at least 6 contiguous amino acids of the $GABA_BR2$ amino acid sequence. By "purified" in reference to a polypeptide is meant that the polypeptide is in a form (*i.e.*, its association with other molecules) distinct from naturally occurring polypeptides. Preferably, the polypeptide has been substantially purified to represent at least 75%, more preferably 85%, most preferably 95% of the total protein present in a preparation. In preferred embodiments, the purified polypeptide has at least 12 contiguous, at least 18 contiguous, at least 54 contiguous, or the entire amino acid sequence of SEQ. ID. NO. 4.

Another aspect of the present invention features a $GABA_BR2$-binding agent comprising a molecule which binds to a polypeptide consisting of the amino acid sequence of SEQ. ID. NO. 4. The binding agent is preferably a purified antibody. Other examples of binding agents include organic compounds which bind to $GABA_BR2$.

By "purified" in reference to a binding agent, such as an antibody, is meant that the binding agent is in a form (*i.e.*, its association with other molecules) distinct from a naturally occurring binding agent, if the binding agent is found in nature. Preferably, the binding agent is an antibody provided as a purified preparation representing at least 1%, more preferably at least 50%, more preferably at least 85%, most preferably at least 95% of the total protein in the preparation.

Another aspect of the present invention describes a method of making a $GABA_BR2$ or a fragment thereof. The method is carried out by incubating recombinant cells containing nucleic acid encoding $GABA_BR2$ or a fragment thereof under conditions where the nucleic acid is expressed.

Another aspect of the present invention describes a method of selecting for compounds able to modulate $GABA_BR$ activity. The method comprises the steps of (a) contacting a recombinant cell functionally expressing $GABA_BR2$ with a first test compound; and (b) measuring the ability of said test compound to affect $GABA_BR$ activity. Compounds modulating $GABA_BR$ activity either evoke a $GABA_BR$ activity, potentiate $GABA_BR$ activity, or inhibit a $GABA_BR$ activity. Cells functionally expressing $GABA_BR2$ also express $GABA_BR1a$ and/or $GABA_BR1b$.

Preferably, the ability of a plurality of different test compounds to affect $GABA_BR$ activity are tested. In preferred

embodiments at least 5, at least 10, at least 50 different compounds, and at least 100 different compounds are tested over a span of one week.

Other aspects of the present invention describe coexpression systems and the use of such systems to measure the activity at, or screen compounds active at, $GABA_BR1a$, $GABA_BR1b$, or $GABA_BR2$, preferably $GABA_BR2$. The coexpression systems comprise at least one of $GABA_BR1a$ and $GABA_BR1b$, $GABA_BR2$, and Gqo5.

Other aspects of the present invention describe coexpression systems and the use of such systems to measure the activity at, or screen compounds active at, $GABA_BR1a$, $GABA_BR1b$, or $GABA_BR2$. The coexpression systems comprise at least one of $GABA_BR1a$ or $GABA_BR1b$, coexpressed with $GABA_BR2$ and Gqo5. The presence of Gqo5 provides for signal transduction swapping allowing for receptor activity to be measured by mobilization of intracellular calcium mediated by the activation of phospholipase C.

Assays using the coexpression systems described above can be used to screen chemical libraries for compounds that modulate $GABA_B$ receptors. For example, in different embodiments, a library of compounds containing 10 or more compounds is screened at once; and 10 or more compounds are individually tested over the course of eight hours.

Preferably, the coexpression system is present in an isolated cell. An "isolated cell" includes tissue cells and refers to a cell present in a different environment (including a different concentration), than it is normally found in nature.

In other aspects, the invention describes transgenic nonhuman mammals containing a transgene encoding $GABA_BR2$, a $GABA_BR2$ fragment, or a derivative thereof; or a gene affecting the expression of $GABA_BR2$; and methods of creating a transgenic nonhuman mammal containing a transgene encoding an $GABA_BR2$, a $GABA_BR2$ fragment, or a derivative thereof.

Various examples are described herein. These examples are not intended in any way to limit the claimed invention.

Other features and advantages of the invention will be apparent from the following drawing, the description of the invention, the examples, and the claims.

BRIEF DESCRIPTION OF DRAWINGS

Figures 1a-1n illustrate the nucleic acid sequences encoding for the human $GABA_BR2$ designated SEQ. ID. NO. 1, human $GABA_BR1a$ designated SEQ. ID. NO. 2, and human $GABA_BR1b$ designated SEQ. ID. NO. 3.

Figures 2a-2f illustrate the amino acid sequences of the human $GABA_BR2$ (SEQ. ID. NO. 4); the rat $GABA_bR1a$ (SEQ. ID. NO. 5); the rat $GABA_bR1b$ protein (SEQ. ID. NO. 6); the human $GABA_bR1a$ (SEQ. ID. NO. 7); and the human $GABA_bR1a$ (SEQ. ID. NO. 8).

Figures 3a-3d provides the human calcium receptor nucleic acid sequence and the encoded for amino acid sequence.

Figure 4 illustrates functional expression of $GABA_BR2$ in *Xenopus* oocytes.

DETAILED DESCRIPTION OF THE INVENTION

The present invention features $GABA_BR2$. $GABA_BR2$ is closely related to $GABA_BR1a$ and $GABA_BR1b$. Nucleic acid encoding for human $GABA_BR2$ has a sequence similarity of about 50% with nucleic acid encoding rat $GABA_BR1a$ and rat $GABA_BR1b$. Human $GABA_BR2$ has a sequence identity of about 40% with rat $GABA_BR1a$ and $GABA_BR1b$ amino acid sequence.

Nucleic acid encoding $GABA_BR2$ was cloned by first identifying a human nucleic acid sequence approximately 38% identical to the nucleic acid sequence of rat $GABA_BR1$. Exact match polymerase chain reaction (PCR) primers were designed based on sequences from the identified sequence and used to amplify human $GABA_BR2$ nucleic acid from a human cerebral cortex cDNA library. A PCR product encoding human $GABA_BR2$ was isolated and cloned.

Northern blot analysis revealed that an approximately 6.3 Kb human $GABA_BR2$ transcript was abundantly expressed in the human brain. Expression was not detected in the heart, placenta, lung, liver, skeletal muscle, kidney or pancreas under conditions where $GABA_BR2$ transcript was identified in the human brain. Within the human brain $GABA_BR2$ is broadly expressed at variable levels.

Compounds modulating $GABA_BR$ activity can be obtained, for example, by screening a group, or library, of compounds to identify those compounds having the desired activity and then synthesizing such compounds. Thus, included in the present

invention is a method of making a $GABA_BR$ active compound by first screening for a compound having desired properties and then chemically synthesizing that compound.

Nucleic Acid Encoding $GABA_BR2$

Nucleic acids encoding $GABA_BR2$ have a variety of different uses including one or more of the following: (1) producing receptor proteins which can be used, for example, for structure determination, to assay a molecule's activity on a receptor, and to obtain $GABA_BR2$ modulatory agents; (2) being sequenced to determine a receptor's nucleotide sequence which can be used, for example, as a basis for comparison with other receptors to determine conserved regions, determine unique nucleotide sequences for normal and altered receptors, and to determine nucleotide sequences to be used as target sites for antisense nucleic acids, ribozymes, hybridization detection probes, or PCR amplification primers; (3) as hybridization detection probes to detect the presence of a native receptor and/or a related receptor in a sample; (4) as PCR primers to generate particular nucleic acid sequence regions, for example, to generate regions to be probed by hybridization detection probes; and (5) to provide an extracellular domain, transmembrane domain, or extracellular domain for use in the construction of a chimeric receptor.

Hybridization probes and primers based on the $GABA_BR2$ sequence information provided herein can be used, for example, to obtain nucleic acid from different sources or to identify the presence of $GABA_BR2$ nucleic acid in a sample. Nucleic acid encoding proteins related to human $GABA_BR2$ can be obtained from human and nonhuman sources. Such related nucleic acids are useful for identifying important $GABA_BR2$ structural motifs and may also provide new therapeutic target sites.

Primer hybridization specificity to target nucleic acid can be adjusted by varying the hybridization conditions. When annealing at higher stringency conditions of 50-60°C, sequences which are greater than about 75% complementarity to the primer will be amplified. By employing lower stringency conditions, annealing at 35-37°C, sequences which are greater than about 40-50% complementarity to the primer will be amplified.

Hybridization assay probes can be designed to detect the presence of a particular nucleic acid target sequence perfectly complementary to the probe and target sequences of lesser complementarity by varying the hybridization conditions and probe design. Factors affecting probe design, such as length, G and C content, possible self-complementarity, and wash conditions, are well known in the art. (See, for example, Sambrook *et al., Molecular Cloning,* Cold Spring Harbor Laboratory Press (1989).) Sambrook *et al., Molecular Cloning,* also discusses the design and use of degenerative probes based on polypeptide sequence information.

Preferably, the nucleic acid probes targeted to $GABA_BR2$ nucleic acid distinguish $GABA_BR2$ nucleic acid from $GABA_B1a$ and $GABA_B1b$ nucleic acid. Such probes are readily designed by comparing the nucleic acid sequences of target $GABA_BR2$, and non-target $GABA_B1a$ and $GABA_B1b$, to obtain probes having proper probe:target and probe:non-target T_m characteristics. Preferably, the probe:target duplex T_m is at least about 5°C greater than the probe:non-target T_m.

Probes specific for a target contain a target complementary region and may also contain target non-complementary regions. The target non-complementary regions, if present, are designed not to affect the specificity of the probe. An example of a target non-complementary region is a nucleic acid sequence used as a capture sequence in a sandwich assay, where the capture sequence does not hybridize to target or non-target nucleic acids. (See, Stabinsky, U.S. Patent No. 4,739,044, and Ranki *et al.*, U.S. Patent No. 4,563,419, both of which are incorporated by reference herein.)

The probes can be used under conditions of proper stringency conditions where target and non-target nucleic acid are distinguished. As the stringency conditions are increased, the complementarity of two nucleic acids required to form a stable duplex is also increased.

As a general guideline, high stringency conditions (*e.g.*, hybridization at 50-65°C, 5X SSPC, 50% formamide, wash at 50-65°C, 0.5X SSPC) can be used to obtain hybridization between nucleic acid sequences having regions which are greater than about 90% complementary. Low stringency conditions (*e.g.*, hybridization at

35-37°C, 5X SSPC, 40-45% formamide, wash at 42°C 1X SSPC) can be used so that sequences having regions greater than 35-45% complementarity will hybridize to the probe.

If desired, nucleic acid probes may be labeled with a detectable label using techniques well known in the art. Examples of detectable labels include radiolabels, enzymes, fluorescent molecules, and chemiluminescent molecules.

Any tissue can be used as a source for genomic DNA. However, with respect to RNA, the most preferred source is tissues which express elevated levels of $GABA_BR2$ or related proteins.

Specific nucleic acids can also be produced enzymatically using a host transformed with a plasmid encoding for the desired nucleic acid. Additionally, standard techniques for chemically synthesizing nucleic acids include solid phase phosphoramidite chemical synthesis.

<u>$GABA_BR2$ polypeptides</u>

$GABA_BR2$ polypeptides made up of $GABA_BR2$, $GABA_BR2$ fragments, and derivatives thereof have different uses including, being used to produce antibodies to determine the presence of the protein, and being used to screen for compounds able to bind to the protein. $GABA_BR2$ polypeptides are preferably produced using recombinant nucleic acid techniques.

Polypeptides can also be synthesized using solid phase techniques. Solid-phase synthesis is commenced from the carboxy-terminal end of the peptide using an α-amino protected amino acid. BOC protective groups can be used for all amino groups even though other protective groups are suitable. For example, BOC-lys-OH can be esterified to chloromethylated polystyrene resin supports. The polystyrene resin support is preferably a copolymer of styrene with about 0.5 to 2% divinylbenzene as a cross-linking agent which causes the polystyrene polymer to be completely insoluble in certain organic solvents. *See* Stewart *et al.*, <u>Solid-Phase Peptide Synthesis</u> (1969), W.H. Freeman Co., San Francisco; and Merrifield, *J. Am. Chem. Soc.* *85*:2149-2154, 1963. These and other methods of peptide synthesis are also exemplified by U.S. Patent Nos. 3,862,925; 3,842,067; 3,972,859; and 4,105,602.

$GABA_BR2$ derivatives, and nucleic acid encoding for $GABA_BR2$ derivatives can be produced using techniques well known in the art based upon the present disclosure. $GABA_BR2$ derivatives have a sequence similarity of at least 70%, more preferably at least 90%, even more preferably at least 95% sequence similarity to the amino acid sequence provided in SEQ. ID. NO. 4. Sequence similarity is preferably determined using BLASTN (Altschul *et al., J. Mol. Biol. 215:*403-410, 1990.)

Examples of specific types of derivatives include amino acid alterations such as deletions, substitutions, additions, and amino acid modifications. A "deletion" refers to the absence of one or more amino acid residue(s) in the related polypeptide. An "addition" refers to the presence of one or more amino acid residue(s) in the related polypeptide. Additions and deletions to a polypeptide may be at the amino terminus, the carboxy terminus, and/or internal. Amino acid "modification" refers to the alteration of a naturally occurring amino acid to produce a non-naturally occurring amino acid. A "substitution" refers to the replacement of one or more amino acid residue(s) by another amino acid residue(s) in the polypeptide. Derivatives can contain different combinations of alterations including more than one alteration and different types of alterations.

While the effect of an amino acid change varies depending upon factors such as phosphorylation, glycosylation, intra-chain linkages, tertiary structure, and the role of the amino acid in the active site or a possible allosteric site, it is generally preferred that the substituted amino acid is from the same group as the amino acid being replaced. To some extent the following groups contain amino acids which are interchangeable: the basic amino acids lysine, arginine, and histidine; the acidic amino acids aspartic and glutamic acids; the neutral polar amino acids serine, threonine, cysteine, glutamine, asparagine and, to a lesser extent, methionine; the nonpolar aliphatic amino acids glycine, alanine, valine, isoleucine, and leucine (however, because of size, glycine and alanine are more closely related and valine, isoleucine and leucine are more closely related); and the aromatic amino acids phenylalanine, tryptophan, and tyrosine. In addition, although classified in different categories, alanine, glycine, and serine seem to be interchangeable to some extent,

and cysteine additionally fits into this group, or may be classified with the polar neutral amino acids.

While proline is a nonpolar neutral amino acid, its replacement represents difficulties because of its effects on conformation. Thus, substitutions by or for proline are not preferred, except when the same or similar conformational results can be obtained. The conformation conferring properties of proline residues may be obtained if one or more of these is substituted by hydroxyproline (Hyp).

Examples of modified amino acids include the following: altered neutral nonpolar amino acids such as ω-amino acids of the formula $H_2N(CH_2)_nCOOH$ where n is 2-6, sarcosine (Sar), t-butylalanine (t-BuAla), t-butylglycine (t-BuGly), N-methyl isoleucine (N-MeIle), and norleucine (Nleu); altered neutral aromatic amino acids such as phenylglycine; altered polar, but neutral amino acids such as citrulline (Cit) and methionine sulfoxide (MSO); altered neutral and nonpolar amino acids such as cyclohexyl alanine (Cha); altered acidic amino acids such as cysteic acid (Cya); and altered basic amino acids such as ornithine (Orn).

Preferred derivatives have one or more amino acid alteration(s) which do not significantly affect the receptor activity of the related receptor protein. In regions of the $GABA_BR2$ not necessary for receptor activity amino acids may be deleted, added or substituted with less risk of affecting activity. In regions required for receptor activity, amino acid alterations are less preferred as there is a greater risk of affecting receptor activity. Such alterations should be conservative alterations. For example, one or more amino acid residues within the sequence can be substituted by another amino acid of a similar polarity which acts as a functional equivalent.

Conserved regions tend to be more important for protein activity than non-conserved regions. Standard procedures can be used to determine the conserved and non-conserved regions important of receptor activity using *in vitro* mutagenesis techniques or deletion analyses and measuring receptor activity as described by the present disclosure.

Derivatives can be produced using standard chemical techniques and recombinant nucleic acid techniques.

Modifications to a specific polypeptide may be deliberate, as through site-directed mutagenesis and amino acid substitution during solid-phase synthesis, or may be accidental such as through mutations in hosts which produce the polypeptide. Polypeptides including derivatives can be obtained using standard techniques such as those described by Sambrook *et al., Molecular Cloning,* Cold Spring Harbor Laboratory Press (1989). For example, Chapter 15 of Sambrook describes procedures for site-directed mutagenesis of cloned DNA.

GABA$_B$R2 Antibodies

Antibodies binding GABA$_B$R2 have various uses such as being used as therapeutic agents to modulate GABA$_B$R activity; as diagnostic tools for determining GABA$_B$R2 number; as research tools for studying receptor synthesis, structure, and function; and as a tool by purifying GABA$_B$R2.

GABA$_B$R2, and GABA$_B$R2 fragments retaining antigenic determinants, can be used to generate antibodies recognizing GABA$_B$R2. Preferably, polypeptide fragments used to generate antibodies are at least six amino acid in length. Both polyclonal and monoclonal antibodies can be generated.

Antibodies can be produced using standard techniques such as those described by Harlow and Lane in *Antibodies, a Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. Sources of immunogens for antibody production include purified GABA$_B$R2, GABA$_B$R2 fragments, and whole cells expressing GABA$_B$R2. The present invention also includes hybridoma cells secreting monoclonal antibodies to GABA$_B$R2.

Recombinant Cells

Nucleic acid expressing a functional GABA$_B$R2 can be used to create transfected cells lines functionally expressing GABA$_B$R2. Such cell lines have a variety of uses such as being used for high-throughput screening for compounds modulating GABA$_B$R activity; being used to assay binding to GABA$_B$R2; and as factories to produce large amounts of GABA$_B$R2, or GABA$_B$R2 fragments.

A variety of cell lines can couple exogenously expressed receptors to endogenous functional responses. Cell lines such as NIH-3T3, HeLa, NG115, CHO, HEK 293 and COS7 which are expected to

lack $GABA_BR2$ can be tested to confirm that they lack an endogenous $GABA_BR2$.

Production of stable transfectants can be accomplished by transfection of an appropriate cell line with an expression vector, such as the eukaryotic pMSG vectors. Expression vectors containing a promoter region, such as the mouse mammary tumor virus promoter (MMTV), drive high-level transcription of cDNAs in a variety of mammalian cells. In addition, these vectors contain genes for selecting cells stably expressing cDNA of interest. The selectable marker in the pMSG vectors encodes an enzyme, xanthine-guanine phosphoribosyl transferase (XGPRT), conferring resistance to a metabolic inhibitor that is added to the culture to kill nontransfected cells.

The most effective method for transfection of eukaryotic cell lines with plasmid DNA varies with the given cell type. The $GABA_BR2$ expression construct will be introduced into cultured cells by the appropriate technique, such as Ca^{2+} phosphate precipitation, DEAE-dextran transfection, lipofection or electroporation. Expression of the $GABA_BR2$ cDNA in cell lines can be assessed by solution hybridization and Northern blot analysis.

Assaying For Compounds Modulating $GABA_BR$ Activity

The ability of compounds to modulate $GABA_BR$ activity can be assayed by measuring alterations of cellular processes affected by $GABA_BR$ activity. Generally, a $GABA_BR2$ agonist is present when measuring antagonist activity. However, protein fusions can be created, for example, where an agonist extracellular binding domain of $GABA_BR2$ is swapped with the agonist binding domain of a different receptor allowing for the measurement of antagonist activity using an agonist of the different receptor; or where the intracellular domain of $GABA_BR2$ is swapped with the intracellular domain of a different receptor allowing for the measuring of $GABA_BR$ activity by measuring intracellular effects caused by the different receptor.

Chimeric proteins are preferably produced using recombinant nucleic acid techniques to provide an appropriate nucleic acid encoding for the chimeric protein. Preferably, portions of $GABA_BR2$ are swapped with portions of the calcium receptor. The $GABA_BR2$ extracellular domain is made up of approximately amino

acids 1-422 Of SEQ. ID. NO. 4, the $GABA_BR2$ transmembrane domain is made up of approximately amino acids 423-686 Of SEQ. ID. NO. 4, and the $GABA_BR2$ intracellular domain is made up of approximately amino acids 687-883 Of SEQ. ID. NO. 4. The human calcium receptor amino acid and encoding nucleic acid is provided in Figure 3. The calcium receptor extracellular domain is made up of approximately amino acids 1-612, the calcium receptor transmembrane domain is made up of approximately amino acids 613-862, and the calcium receptor intracellular domain is made up of approximately amino acids 863-1078. Calcium receptor activity can be measured using techniques well known in the art such as those described by Brown *et al.*, U.S. Patent No. 5,688,938, hereby incorporated by reference herein.

Binding Assays

The present invention also includes using $GABA_BR2$ and fragments thereof in binding assays. Binding assays can be carried out using techniques well known in the art. Binding assays preferably employ radiolabeled binding agents.

An example of a binding assay is carried out by first attaching $GABA_BR2$, or a fragment thereof, to a solid-phase support to create an affinity matrix. The affinity matrix is then contacted with potential $GABA_BR2$ binding agents. A large library of compounds may be used to determine those compounds binding to the affinity matrix. Bound compounds can be eluted from the column.

Transgenic Animals

The present invention also concerns the construction and use of transgenic animals, and transformed cells, encoding $GABA_BR2$. Transgenic nonhuman mammals are particularly useful as an *in vivo* test system for studying the effects of introducing $GABA_BR2$; regulating the expression of $GABA_BR2$ (*e.g.*, through the introduction of additional genes, antisense nucleic acids, or ribozymes); and studying the effect of compounds which mimic or block the effect of $GABA_BR2$.

Experimental model systems for studying the physiological role of the $GABA_BR2$ can be created having varying degrees of

receptor expression. For example, nucleic acid encoding a receptor may be inserted into cells naturally expressing the receptor such that the gene is expressed at much higher levels. Alternatively, a recombinant gene may be used to inactivate the endogenous gene by homologous recombination and, thereby, create an $GABA_BR2$ deficient cell, tissue, or animal.

Inactivation of a gene can be caused, for example, by using a recombinant gene engineered to contain an insertional mutation (*e.g.*, the *neo* gene). The recombinant gene is inserted into the genome of a recipient cell, tissue or animal, and inactivates transcription of the receptor. Such a construct may be introduced into a cell, such as an embryonic stem cell, by techniques such as transfection, transduction, and injection. Stem cells lacking an intact receptor sequence may generate transgenic animals deficient in the receptor.

Preferred test models are transgenic animals. A transgenic animal has cells containing DNA which has been artificially inserted into a cell and inserted into the genome of the animal which develops from that cell. Preferred transgenic animals are primates, mice, rats, cows, pigs, horses, goats, sheep, dogs and cats.

A variety of methods are available for producing transgenic animals. For example, DNA can be injected into the pronucleus of a fertilized egg before fusion of the male and female pronuclei, or injected into the nucleus of an embryonic cell (*e.g.*, the nucleus of a two-cell embryo) following the initiation of cell division (Brinster *et al.*, *Proc. Nat. Acad. Sci. USA 82*: 4438-4442, 1985). By way of another example, embryos can be infected with viruses, especially retroviruses, modified to carry $GABA_BR2$ nucleotide sequences.

Pluripotent stem cells derived from the inner cell mass of the embryo and stabilized in culture can be manipulated in culture to incorporate nucleotide sequences of the invention. A transgenic animal can be produced from such stem cells through implantation into a blastocyst that is implanted into a foster mother and allowed to come to term. Animals suitable for transgenic experiments can be obtained from standard commercial sources such as Charles River (Wilmington, MA), Taconic (Germantown, NY), and Harlan Sprague Dawley (Indianapolis, IN).

Methods for the culturing of embryonic stem (ES) cells and the subsequent production of transgenic animals by the introduction of DNA into ES cells using methods such as electroporation, calcium phosphate/DNA precipitation and direct injection are well known to those of ordinary skill in the art. See, for example, Teratocarcinomas and Embryonic Stem Cells, A Practical Approach, E.J. Robertson, ed., IRL Press (1987).

Procedures for embryo manipulations are well known in the art. Procedures for manipulating rodent embryo and for microinjecting DNA into the pronucleus of the zygote are well known in the art. Microinjection procedures for fish, amphibian eggs and birds are well known in the art and are described, for example, in Houdebine and Chourrout, *Experientia 47*: 897-905, 1991. Procedures for introducing DNA into tissues of animals are well known in the art and are described, for example, in U.S. Patent No. 4,945,050.

Transfection and isolation of desired clones can be carried out using standard techniques (*e.g.,* E.J. Robertson, *supra*). For example, random gene integration can be carried out by co-transfecting nucleic acid with a gene encoding antibiotic resistance. Alternatively, for example, the gene encoding antibiotic resistance is physically linked to a nucleic acid sequence encoding $GABA_BR2$.

DNA molecules introduced into ES cells can also be integrated into the chromosome through the process of homologous recombination. (*E.g.,* Capecchi, *Science 244*: 1288-1292, 1989.) Methods for positive selection of the recombination event (*e.g.,* neomycin resistance) and dual positive-negative selection (*e.g.,* neomycin resistance and gancyclovir resistance) and the subsequent identification of the desired clones by PCR have been described in references such as Capecchi, *supra* and Joyner *et al., Nature 338*:153-156, 1989, which is hereby incorporated by reference herein.

The final phase of the procedure is to inject targeted ES cells into blastocysts and to transfer the blastocysts into pseudopregnant females. The resulting chimeric animals are bred and the offspring are analyzed by Southern blotting to identify individuals carrying the transgene.

An example describing the preparation of a transgenic mouse

is as follows. Female mice are induced to superovulate and placed with males. The mated females are sacrificed by CO_2 asphyxiation or cervical dislocation and embryos are recovered from excised oviducts. Surrounding cumulus cells are removed. Pronuclear embryos are then washed and stored until the time of injection.

Randomly cycling adult female mice paired with vasectomized males serve as recipients for implanted embryos. Recipient females are mated at the same time as donor females and embryos are transferred surgically to recipient females.

Procedures for generating transgenic rats are similar to that of mice. (*E.g.,* Hammer *et al.*, Cell 63:1099-1112, 1990.) Procedures for producing transgenic non-rodent mammals and other animals are well known in art. (*E.g.,* Houdebine and Chourrout, *supra;* Pursel *et al., Science 244*:1281-1288, 1989; and Simms *et al., Bio/Technology 6*:179-183, 1988.)

Therapeutic Modulation

Different types of diseases and disorders can be treated using compounds modulating $GABA_BR$ activity. Additionally, such compounds can be used prophylactically. Compounds modulating $GABA_BR$ activity can be administered to patients who would benefit from such treatment. Patients are mammals, preferably humans.

Modulating $GABA_BR$ activity can be carried to achieve useful therapeutic effects such as preventing or treating one or more of the following: spasticity and motor control disorders using $GABA_BR$ agonists; pain, using $GABA_BR$ antagonists; cognitive disorders using $GABA_BR$ antagonists; neurological disorders such as Alzheimer's disease and Huntington's disease; psychiatric disorders, such as depression using $GABA_BR$ agonists; alcohol dependence and withdrawal using $GABA_BR$ antagonists; feeding behavior; cardiovascular and respiratory disorders with antagonists exerting an excitatory effect and agonists depressing inspiratory neurons; and peripheral function disorders.

Modulators of $GABA_BR$ activity can be administered to a patient using standard techniques. Techniques and formulations generally may be found in Remington's Pharmaceutical Sciences, 18^{th} ed., Mack Publishing Co., Easton, PA, 1990 (hereby incorporated by reference herein).

Suitable dosage forms, in part, depend upon the use or the route of entry, for example, oral, transdermal, transmucosal, or by injection (parenteral). Such dosage forms should allow the therapeutic agent to reach a target cell whether the target cell is present in a multicellular host or in culture. For example, pharmacological compounds or compositions injected into the blood stream should be soluble. Other factors are well known in the art, and include considerations such as toxicity and dosage forms which retard the therapeutic agent from exerting its effect.

Therapeutic compounds can be formulated as pharmaceutically acceptable salts and complexes thereof. Pharmaceutically acceptable salts are non-toxic salts in the amounts and concentrations at which they are administered. The preparation of such salts can facilitate the pharmacological use by altering the physical characteristics of the compound without preventing it from exerting its physiological effect. Useful alterations in physical properties include lowering the melting point to facilitate transmucosal administration and increasing the solubility to facilitate administering higher concentrations of the drug.

The pharmaceutically acceptable salt of a compound may be present as a complex. Examples of complexes include an 8-chlorotheophylline complex (analogous to, *e.g.*, dimenhydrinate:diphenhydramine 8-chlorotheophylline (1:1) complex; Dramamine) and various cyclodextrin inclusion complexes.

Pharmaceutically acceptable salts include acid addition salts such as those containing sulfate, hydrochloride, fumarate, maleate, phosphate, sulfamate, acetate, citrate, lactate, tartrate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, cyclohexylsulfamate and quinate.

Pharmaceutically acceptable salts can be obtained from acids such as hydrochloric acid, maleic acid, sulfuric acid, phosphoric acid, sulfamic acid, acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, cyclohexylsulfamic acid, fumaric acid, and quinic acid. Pharmaceutically acceptable salts also include basic addition salts such as those containing benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine,

aluminum, calcium, lithium, magnesium, potassium, sodium, ammonium, alkylamine, and zinc, when acidic functional groups, such as carboxylic acid or phenol are present. For example, see Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing Co., Easton, PA, p. 1445, 1990. Such salts can be prepared using the appropriate corresponding bases.

Carriers or excipients can also be used to facilitate administration of therapeutic agents. Examples of carriers include calcium carbonate, calcium phosphate, various sugars such as lactose, glucose, or sucrose, or types of starch, cellulose derivatives, gelatin, vegetable oils, polyethylene glycols and physiologically compatible solvents. Examples of physiologically compatible solvents include sterile solutions of water for injection (WFI), saline solution and dextrose.

$GABA_BR$ modulating compounds can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical (transdermal), or transmucosal administration. For systemic administration, oral administration is preferred. For oral administration, for example, the compounds can be formulated into conventional oral dosage forms such as capsules, tablets, and liquid preparations such as syrups, elixirs, and concentrated drops.

Alternatively, injection (parenteral administration) may be used, *e.g.*, intramuscular, intravenous, intraperitoneal, and subcutaneous. For injection, compounds are formulated in liquid solutions, preferably, in physiologically compatible buffers or solutions, such as saline solution, Hank's solution, or Ringer's solution. In addition, the compounds may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms can also be produced.

Systemic administration can be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are well known in the art, and include, for example, for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration, for example, may be through nasal sprays, rectal suppositories, or vaginal suppositories.

For topical administration, compounds can be formulated into ointments, salves, gels, or creams, as is well known in the art.

The amounts of various $GABA_BR$ modulating compounds to be administered can be determined by standard procedures taking into account factors such as the compound IC_{50}, EC_{50}, the biological half-life of the compound, the age, size and weight of the patient, and the disease or disorder associated with the patient. The importance of these and other factors to be considered are well known to those of ordinary skill in the art. Generally, the amount is expected to preferably be between about 0.01 and 50 mg/kg of the animal to be treated.

EXAMPLES

The example provided below illustrates different aspects and embodiments of the present invention. The example is not intended to limit the claimed invention.

Functional expression of $GABA_BR2$

Xenopus oocytes were co-injected with *in vitro* transcribed RNA (7 ng) encoding $GABA_BR1a$, $GABA_BR2$ and chimeric Gqo5. Chimeric Gqo5 is described in *Nature 363*:274-276, 1993. Coexpression of the different proteins was employed because $GABA_BR$ functions as a heterodimer of the subunits $GABA_BR1$ or $GABA_BR2$ (Jones *et al. Nature 396*:674-679, 1998). Following a 72 hour incubation, the oocytes were voltage clamped using standard electrophysiological techniques (Hille, B., Ionic Channels of Excitable membranes, pp. 30-33, Sinauer Associates, Inc., Sunderland, MA, 1992). Activation of the receptor heterodimers was detected by increases in the calcium-activated chloride current.

Application of the $GABA_B$ receptor agonist baclofen caused dose-dependent, reversible, oscillatory increases in the calcium-activated chloride current as shown in Figure 4, with an EC_{50} of approximately 1 µM. These responses were completely blocked by the competitive $GABA_B$ receptor antagonist SCH 50911 (100 µM). Oocytes expressing $GABA_B$ receptor heterodimers with the inwardly rectifying potassium channels (GIRKS; Kir3.1/3.2/3.4) were used as the positive control (Jones *et al.*, *Nature 396*:674-679, 1998.) Thus, the use of the chimeric G-Protein Gqo5 promotes signal transduction through mobilization of intracellular calcium.

Other embodiments are within the following claims. Thus, while several embodiments have been shown and described, various modifications may be made, without departing from the spirit and scope of the present invention.

Claims

1. A purified nucleic acid comprising at least 18 contiguous nucleotides of a nucleic acid sequence provided in SEQ ID NO: 1.

2. The purified nucleic acid of claim 1, comprising at least 27 contiguous nucleotides of the nucleic acid sequence provided in SEQ ID NO: 1.

3. The purified nucleic acid of claim 2, comprising at least 45 contiguous nucleotides of the nucleic acid sequence provided in SEQ ID NO: 1.

4. The purified nucleic acid of claim 3, comprising the nucleic acid sequence provided in SEQ ID NO: 1.

5. A purified nucleic acid comprising a nucleic acid sequence encoding at least 6 contiguous amino acids of an amino acid sequence provided in SEQ. ID. NO: 4.

6. The purified nucleic acid of claim 5, wherein said nucleic acid encodes at least 12 contiguous amino acids of the amino acid sequence provided in SEQ. ID. NO: 4.

7. The purified nucleic acid of claim 6, wherein said nucleic acid encodes at least 18 contiguous amino acids of the amino acid sequence provided in SEQ. ID. NO: 4.

8. The purified nucleic acid of claim 7, wherein said nucleic acid encodes at least 54 contiguous amino acids of the amino acid sequence provided in SEQ. ID. NO: 4.

9. The purified nucleic acid of claim 8, wherein said nucleic acid encodes the amino acid sequence provided in SEQ. ID. NO: 4.

10. The purified nucleic acid of any of claims 1-9, wherein said nucleic acid is substantially purified.

11. The purified nucleic acid of any of claims 1-9, wherein said nucleic acid is recombinant nucleic acid which is part of an expression vector.

12. The purified nucleic acid of any of claims 1-9, wherein said nucleic acid is transcriptionally coupled to an exogenous promoter.

13. A recombinant cell comprising the expression vector of claim 11.

14. A recombinant cell made by a process comprising the step of introducing the nucleic acid of any one of claims 1-12 into a cell.

15. A purified nucleic acid comprising a nucleotide sequence of 20 contiguous nucleotides of which at least 18 nucleotides are complementary to the nucleic acid sequence provided in SEQ ID NO: 1 or the perfect complement of SEQ ID NO: 1.

16. The nucleic acid of claim 15, wherein said purified nucleic acid comprises a nucleotide sequence of 20 contiguous nucleotides which has at least 19 bases complementary to the nucleic acid sequence provided in SEQ ID NO: 1 or the perfect complement of SEQ ID NO: 1.

17. The nucleic acid of claim 16, wherein said purified nucleic acid comprises a nucleotide sequence of 20 contiguous nucleotides which is complementary to the nucleic acid sequence provided in SEQ ID NO: 1 or the perfect complement of SEQ ID NO: 1.

18. A purified polypeptide comprising at least 6 contiguous amino acids of an amino acid sequence provided in SEQ. ID. NO: 4.

19. The purified polypeptide of claim 18, comprising at least 12 contiguous amino acids of the amino acid sequence

provided in SEQ. ID. NO: 4.

20. The purified polypeptide of claim 19, comprising at least 18 contiguous amino acids of the amino acid sequence provided in SEQ. ID. NO: 4.

21. The purified polypeptide of claim 20, comprising at least 54 contiguous amino acids of the amino acid sequence provided in SEQ. ID. NO: 4.

22. The purified polypeptide of claim 21, consisting of the amino acid sequence provided in SEQ. ID. NO: 4.

23. The polypeptide of any one of claims 18-22, wherein said polypeptide is substantially purified.

24. A purified $GABA_BR2$-binding agent comprising a molecule which binds to a polypeptide consisting of the amino acid sequence of SEQ. ID. NO: 4.

25. The binding agent of claim 24, wherein said binding agent is an antibody.

26. A method of making a $GABA_BR2$ or fragment thereof comprising the step of incubating the recombinant cells of claim 13 under conditions wherein the nucleic acid encoding for the $GABA_BR2$ is expressed.

27. The method of claim 26, further comprising the step of purifying said $GABA_BR2$ or fragment thereof.

28. A method of selecting for a compound modulating $GABA_BR$ activity comprising the steps of

a) contacting a recombinant cell functionally expressing $GABA_BR2$ with a first test compound; and

b) measuring the ability of said test compound to affect $GABA_BR$ activity to select for said compound modulating $GABA_BR$ activity.

29. The method of claim 28, wherein the ability of a plurality of different test compounds to affect $GABA_BR$ activity are tested to select for said compound modulating $GABA_BR$ activity.

30. A coexpression system comprising

a) a cell;

b) at least one of $GABA_BR1a$ and $GABA_BR1b$, which is present in said cell;

c) $GABA_BR2$, which is present in said cell; and

d) Gqo5, which is present in said cell.

31. A method of screening for one or more compounds active at $GABA_BR1a$, $GABA_BR1b$, or $GABA_BR2$ comprising the steps of contacting the coexpression system of claim 30 with at least one of said compounds and measuring the ability of said compounds to effect the mobilization of intracellular calcium.

32. The method of claim 31, wherein 10 or more compounds are individually tested for their ability to effect the mobilization of intracellular calcium over the course of 8 hours.

33. A transgenic nonhuman mammal comprising a nonhuman mammal and a recombinant nucleic acid encoding a polypeptide comprising 6 contiguous amino acids of an amino acid sequence provided in SEQ. ID. NO: 4.

ClustalW Formatted Alignments

SEQ. ID. NO.1	A T G G C T T C C C C G C G G A G C T C C G G G C
SEQ. ID. NO. 2	A T G T T G C T G C T G C T G C T A C T G G C G C
SEQ. ID. NO. 3	A T G G G G C C C G G G G C C C C T T T T G C C C
SEQ. ID. NO.1	A G C C C G G G C C G C G C C G C C G C C G C C A
SEQ. ID. NO. 2	C A C T C T T C C T C C G C C C C C C G G G C G C
SEQ. ID. NO. 3	G G G T G G G G T G G C C A C T G C C G C T T C T
SEQ. ID. NO.1	C C G C C G C C C G C G C G C C T G C T A C T G C
SEQ. ID. NO. 2	G G G C G G G G C G C A G A C C C C C A A C G C C
SEQ. ID. NO. 3	G G T T G T G A T G G C G G C A G G G G T G G C T
SEQ. ID. NO.1	T A C T G C T G C T G C C G C T G C T G C T G C C
SEQ. ID. NO. 2	A C C T C A G A A G G T T G C C A G A T C A T A C
SEQ. ID. NO. 3	C C G G T G T G G G C C T C C C A C T C C C C C C
SEQ. ID. NO.1	T C T G G C G C C C G G G G C C T G G G G C T G G
SEQ. ID. NO. 2	A C C C G C C C T G G G A A G G G G G C A T C A G
SEQ. ID. NO. 3	A T C T C C C G C G G C C T C A C T C G C G G G T
SEQ. ID. NO.1	G C G C G G G G C G C C C C C C G G C C G C C G C
SEQ. ID. NO. 2	G T A C C G G G G C C T G A C T C G G G A C C A G
SEQ. ID. NO. 3	C C C C C C G C A C C C C T C C T C A G A A C G G
SEQ. ID. NO.1	C C A G C A G C C C G C C G C T C T C C A T C A T
SEQ. ID. NO. 2	G T G A A G G C T A T C A A C T T C C T G C C A G
SEQ. ID. NO. 3	C G C G C A G T G T A C A T C G G G G C A C T G T
SEQ. ID. NO.1	G G G C C T C A T G C C G C T C A C C A A G G A G
SEQ. ID. NO. 2	T G G A C T A T G A G A T T G A G T A T G T G T G
SEQ. ID. NO. 3	T T C C C A T G A G C G G G G G C T G G C C A G G
SEQ. ID. NO.1	G T G G C C A A G G G C A G C A T C G G G C G C G
SEQ. ID. NO. 2	C C G G G G G G A G C G C G A G G T G G T G G G G
SEQ. ID. NO. 3	G G G C C A G G C C T G C C A G C C C G C G G T G

FIG. 1a.

SEQ. ID. NO.1 G T G T G C T C C C C G C C G T G G A A C T G G C
SEQ. ID. NO. 2 C C C A A G G T C C G C A A G T G C C T G G C C A
SEQ. ID. NO. 3 G A G A T G G C G C T G G A G G A C G T G A A T A

SEQ. ID. NO.1 C A T C G A G C A G A T C C G C A A C G A G T C A
SEQ. ID. NO. 2 A C G G C T C C T G G A C A G A T A T G G A C A C
SEQ. ID. NO. 3 G C C G C A G G G A C A T C C T G C C G G A C T A

SEQ. ID. NO.1 C T C C T G C G C C C C T A C T T C C T C G A C C
SEQ. ID NO. 2 A C C C A G C C G C T G T G T C C G A A T C T G C
SEQ. ID. NO. 3 T G A G C T C A A G C T C A T C C A C C A C G A C

SEQ. ID. NO.1 T G C G G C T C T A T G A C A C G G A G T G C G A
SEQ. ID. NO. 2 T C C A A G T C T T A T T T G A C C C T G G A A A
SEQ. ID. NO. 3 A G C A A G T G T G A T C C A G G C C A A G C C A

SEQ. ID. NO.1 C A A C G C A A A A G G G T T G A A A G C C T T C
SEQ. ID. NO. 2 A T G G G A A G G T T T T C C T G A C G G G T G G
SEQ. ID. NO. 3 C C A A G T A C C T A T A T G A G C T G C T C T A

SEQ. ID. NO.1 T A C G A T G C A A T A A A A T A C G G G C C G A
SEQ. ID. NO. 2 G G A C C T C C C A G C T C T G G A C G G A G C C
SEQ. ID. NO. 3 C A A C G A C C C T A T C A A G A T C A T C C T T

SEQ. ID. NO.1 A C C A C T T G A T G G T G T T T G G A G G C G T
SEQ. ID. NO. 2 C G G G T G G A T T T C C G G T G T G A C C C C G
SEQ. ID. NO. 3 A T G C C T G G C T G C A G C T C T G T C T C C A

SEQ. ID. NO.1 C T G T C C A T C C G T C A C A T C C A T C A T T
SEQ. ID. NO. 2 A C T T C C A T C T G G T G G G C A G C T C C C G
SEQ. ID. NO. 3 C G C T G G T G G C T G A G G C T G C T A G G A T

SEQ. ID. NO.1 G C A G A G T C C C T C C A A G G C T G G A A T C
SEQ. ID. NO. 2 G A G C A T C T G T A G T C A G G G C C A G T G G
SEQ. ID. NO. 3 G T G G A A C C T C A T T G T G C T T T C C T A T

SEQ. ID. NO.1 T G G T G C A G C T T T C T T T T G C T G C A A C
SEQ. ID. NO. 2 A G C A C C C C C A A G C C C C A C T G C C A G G
SEQ. ID. NO. 3 G G C T C C A G C T C A C C A G C C C T G T C A A

FIG. 1b.

SEQ. ID. NO.1 C A C G C C T G T T C T A G C C G A T A A G A A A
SEQ. ID. NO. 2 T G A A T C G A A C G C C A C A C T C A G A A C G
SEQ. ID. NO. 3 A C C G G C A G C G T T T C C C C A C T T T C T T

SEQ. ID. NO.1 A A A T A C C C T T A T T T C T T T C G G A C C G
SEQ. ID. NO. 2 G C G C G C A G T G T A C A T C G G G G C A C T G
SEQ. ID. NO. 3 C C G A A C G C A C C C A T C A G C C A C A C T C

SEQ. ID. NO.1 T C C C A T C A G A C A A T G C G G T G A A T C C
SEQ. ID. NO. 2 T T T C C C A T G A G C G G G G G C T G G C C A G
SEQ. ID. NO. 3 C A C A A C C C T A C C C G C G T G A A A C T C T

SEQ. ID. NO.1 A G C C A T T C T G A A G T T G C T C A A G C A C
SEQ. ID. NO. 2 G G G G C C A G G C C T G C C A G C C C G C G G T
SEQ. ID. NO. 3 T T G A A A A G T G G G G C T G G A A G A A G A T

SEQ. ID. NO.1 T A C C A G T G G A A G C G C G T G G G C A C G C
SEQ. ID. NO. 2 G G A G A T G G C G C T G G A G G A C G T G A A T
SEQ. ID. NO. 3 T G C T A C C A T C C A G C A G A C C A C T G A G

SEQ. ID. NO.1 T G A C G C A A G A C G T T C A G A G G T T C T C
SEQ. ID. NO. 2 A G C C G C A G G G A C A T C C T G C C G G A C T
SEQ. ID. NO. 3 G T C T T C A C T T C G A C T C T G G A C G A C C

SEQ. ID. NO.1 T G A G G T G C G G A A T G A C C T G A C T G G A
SEQ. ID. NO. 2 A T G A G C T C A A G C T C A T C C A C C A C G A
SEQ. ID. NO. 3 T G G A G G A A C G A G T G A A G G A G G C T G G

SEQ. ID. NO.1 G T T C T G T A T G G C G A G G A C A T T G A G A
SEQ. ID. NO. 2 C A G C A A G T G T G A T C C A G G C C A A G C C
SEQ. ID. NO. 3 A A T T G A G A T T A C T T T C C G C C A G A G T

SEQ. ID. NO.1 T T T C A G A C A C C G A G A G C T T C T C C A A
SEQ. ID. NO. 2 A C C A A G T A C C T A T A T G A G C T G C T C T
SEQ. ID. NO. 3 T T C T T C T C A G A T C C A G C T G T G C C C G

SEQ. ID. NO.1 C G A T C C C T G T A C C A G T G T C A A A A A G
SEQ. ID. NO. 2 A C A A C G A C C C T A T C A A G A T C A T C C T
SEQ. ID. NO. 3 T C A A A A A C C T G A A G C G C C A G G A T G C

FIG. 1c.

SEQ. ID. NO.1 C T G A A G G G G A A T G A T G T G C G G A T C A
SEQ. ID. NO. 2 T A T G C C T G G C T G C A G C T C T G T C T C C
SEQ. ID. NO. 3 C C G A A T C A T C G T G G G A C T T T T C T A T

SEQ. ID. NO.1 T C C T T G G C C A G T T T G A C C A G A A T A T
SEQ. ID. NO. 2 A C G C T G G T G G C T G A G G C T G C T A G G A
SEQ. ID. NO. 3 G A G A C T G A A G C C C G G A A A G T T T T T T

SEQ. ID. NO.1 G G C A G C A A A A G T G T T C T G T T G T G C A
SEQ. ID. NO. 2 T G T G G A A C C T C A T T G T G C T T T C C T A
SEQ. ID. NO. 3 G T G A G G T G T A C A A G G A G C G T C T C T T

SEQ. ID. NO.1 T A C G A G G A G A A C A T G T A T G G T A G T A
SEQ. ID. NO. 2 T G G C T C C A G C T C A C C A G C C C T G T C A
SEQ. ID. NO. 3 T G G G A A G A A G T A C G T C T G G T T C C T C

SEQ. ID. NO.1 A A T A T C A G T G G A T C A T T C C G G G C T G
SEQ. ID. NO. 2 A A C C G G C A G C G T T T C C C C A C T T T C T
SEQ. ID. NO. 3 A T T G G G T G G T A T G C T G A C A A T T G G T

SEQ. ID. NO.1 G T A C G A G C C T T C T T G G T G G G A G C A G
SEQ. ID. NO. 2 T C C G A A C G C A C C C A T C A G C C A C A C T
SEQ. ID. NO. 3 T C A A G A T C T A C G A C C C T T C T A T C A A

SEQ. ID. NO.1 G T G C A C A C G G A A G C C A A C T C A T C C C
SEQ. ID. NO. 2 C C A C A A C C C T A C C C G C G T G A A A C T C
SEQ. ID. NO. 3 C T G C A C A G T G G A T G A G A T G A C T G A G

SEQ. ID. NO.1 G C T G C C T C C G G A A G A A T C T G C T T G C
SEQ. ID. NO. 2 T T T G A A A A G T G G G G C T G G A A G A A G A
SEQ. ID. NO. 3 G C G G T G G A G G G C C A C A T C A C A A C T G

SEQ. ID. NO.1 T G C C A T G G A G G G C T A C A T T G G C G T G
SEQ. ID. NO. 2 T T G C T A C C A T C C A G C A G A C C A C T G A
SEQ. ID. NO. 3 A G A T T G T C A T G C T G A A T C C T G C C A A

SEQ. ID. NO.1 G A T T T C G A G C C C C T G A G C T C C A A G C
SEQ. ID. NO. 2 G G T C T T C A C T T C G A C T C T G G A C G A C
SEQ. ID. NO. 3 T A C C C G C A G C A T T T C C A A C A T G A C A

FIG. 1d.

SEQ. ID. NO.1	A G A T C A A G A C C A T C T C A G G A A A G A C
SEQ. ID. NO. 2	C T G G A G G A A C G A G T G A A G G A G G C T G
SEQ. ID. NO. 3	T C C C A G G A A T T T G T G G A G A A A C T A A
SEQ. ID. NO.1	T C C A C A G C A G T A T G A G A G A G A G T A C
SEQ. ID. NO. 2	G A A T T G A G A T T A C T T T C C G C C A G A G
SEQ. ID. NO. 3	C C A A G C G A C T G A A A A G A C A C C C T G A
SEQ. ID. NO.1	A A C A A C A A G C G G T C A G G C G T G G G G C
SEQ. ID. NO. 2	T T T C T T C T C A G A T C C A G C T G T G C C C
SEQ. ID. NO. 3	G G A G A C A G G A G G C T T C C A G G A G G C A
SEQ. ID. NO.1	C C A G C A A G T T C C A C G G G T A C G C C T A
SEQ. ID. NO. 2	G T C A A A A A C C T G A A G C G C C A G G A T G
SEQ. ID. NO. 3	C C G C T G G C C T A T G A T G C C A T C T G G G
SEQ. ID. NO.1	C G A T G G C A T C T G G G T C A T C G C C A A G
SEQ. ID. NO. 2	C C C G A A T C A T C G T G G G A C T T T T C T A
SEQ. ID. NO. 3	C C T T G G C A C T G G C C C T G A A C A A G A C
SEQ. ID. NO.1	A C A C T G C A G A G G G C C A T G G A G A C A C
SEQ. ID. NO. 2	T G A G A C T G A A G C C C G G A A A G T T T T T
SEQ. ID. NO. 3	A T C T G G A G G A G G C G G C C G T T C T G G T
SEQ. ID. NO.1	T G C A T G C C A G C A G C C G G C A C C A G C G
SEQ. ID. NO. 2	T G T G A G G T G T A C A A G G A G C G T C T C T
SEQ. ID. NO. 3	G T G C G C C T G G A G G A C T T C A A C T A C A
SEQ. ID. NO.1	G A T C C A G G A C T T C A A C T A C A C G G A C
SEQ. ID. NO. 2	T T G G G A A G A A G T A C G T C T G G T T C C T
SEQ. ID. NO. 3	A C A A C C A G A C C A T T A C C G A C C A A A T
SEQ. ID. NO.1	C A C A C G C T G G G C A G G A T C A T C C T C A
SEQ. ID. NO. 2	C A T T G G G T G G T A T G C T G A C A A T T G G
SEQ. ID. NO. 3	C T A C C G G G C A A T G A A C T C T T C G T C C
SEQ. ID. NO.1	A T G C C A T G A A C G A G A C C A A C T T C T T
SEQ. ID. NO. 2	T T C A A G A T C T A C G A C C C T T C T A T C A
SEQ. ID. NO. 3	T T T G A G G G T G T C T C T G G C C A T G T G G

FIG. 1e.

SEQ. ID. NO.1	C G G G G T C A C G G G T C A A G T T G T A T T C
SEQ. ID. NO. 2	A C T G C A C A G T G G A T G A G A T G A C T G A
SEQ. ID. NO. 3	T G T T T G A T G C C A G C G G C T C T C G G A T
SEQ. ID. NO.1	C G G A A T G G G G A G A G A A T G G G G A C C A
SEQ. ID. NO. 2	G G C G G T G G A G G G C C A C A T C A C A A C T
SEQ. ID. NO. 3	G G C A T G G A C G C T T A T C G A G C A G C T T
SEQ. ID. NO.1	T T A A A T T T A C T C A A T T T C A A G A C A G
SEQ. ID. NO. 2	G A G A T T G T C A T G C T G A A T C C T G C C A
SEQ. ID. NO. 3	C A G G G T G G C A G C T A C A A G A A G A T T G
SEQ. ID. NO.1	C A G G G A G G T G A A G G T G G G A G A G T A C
SEQ. ID. NO. 2	A T A C C C G C A G C A T T T C C A A C A T G A C
SEQ. ID. NO. 3	G C T A C T A T G A C A G C A C C A A G G A T G A
SEQ. ID. NO.1	A A C G C T G T G G C C G A C A C A C T G G A G A
SEQ. ID. NO. 2	A T C C C A G G A A T T T G T G G A G A A A C T A
SEQ. ID. NO. 3	T C T T T C C T G G T C C A A A A C A G A T A A A
SEQ. ID. NO.1	T C A T C A A T G A C A C C A T C A G G T T C C A
SEQ. ID. NO. 2	A C C A A G C G A C T G A A A A G A C A C C C T G
SEQ. ID. NO. 3	T G G A T T G G A G G G T C C C C C C C A G C T G
SEQ. ID. NO.1	A G G A T C C G A A C C A C C A A A A G A C A A G
SEQ. ID. NO. 2	A G G A G A C A G G A G G C T T C C A G G A G G C
SEQ. ID. NO. 3	A C C A G A C C C T G G T C A T C A A G A C A T T
SEQ. ID. NO.1	A C C A T C A T C C T G G A G C A G C T G C G G A
SEQ. ID. NO. 2	A C C G C T G G C C T A T G A T G C C A T C T G G
SEQ. ID. NO. 3	C C G C T T C C T G T C A C A G A A A C T C T T T
SEQ. ID. NO.1	A G A T C T C C C T A C C T C T C T A C A G C A T
SEQ. ID. NO. 2	G C C T T G G C A C T G G C C C T G A A C A A G A
SEQ. ID. NO. 3	A T C T C C G T C T C A G T T C T C T C C A G C C
SEQ. ID. NO.1	C C T C T C T G C C C T C A C C A T C C T C G G G
SEQ. ID. NO. 2	C A T C T G G A G G A G G C G G C C G T T C T G G
SEQ. ID. NO. 3	T G G G C A T T G T C C T A G C T G T T G T C T G

FIG. 1f.

SEQ. ID. NO.1	A T G A T C A T G G C C A G T G C T T T T C T C T
SEQ. ID. NO. 2	T G T G C G C C T G G A G G A C T T C A A C T A C
SEQ. ID. NO. 3	T C T G T C C T T T A A C A T C T A C A A C T C A
SEQ. ID. NO.1	T C T T C A A C A T C A A G A A C C G G A A T C A
SEQ. ID. NO. 2	A A C A A C C A G A C C A T T A C C G A C C A A A
SEQ. ID. NO. 3	C A T G T C C G T T A T A T C C A G A A C T C A C
SEQ. ID. NO.1	G A A G C T C A T A A A G A T G T C G A G T C C A
SEQ. ID. NO. 2	T C T A C C G G G C A A T G A A C T C T T C G T C
SEQ. ID. NO. 3	A G C C C A A C C T G A A C A A C C T G A C T G C
SEQ. ID. NO.1	T A C A T G A A C A A C C T T A T C A T C C T T G
SEQ. ID. NO. 2	C T T T G A G G G T G T C T C T G G C C A T G T G
SEQ. ID. NO. 3	T G T G G G C T G C T C A C T G G C T T T A G C T
SEQ. ID. NO.1	G A G G G A T G C T C T C C T A T G C T T C C A T
SEQ. ID. NO. 2	G T G T T T G A T G C C A G C G G C T C T C G G A
SEQ. ID. NO. 3	G C T G T C T T C C C C C T G G G G C T C G A T G
SEQ. ID. NO.1	A T T T C T C T T T G G C C T T G A T G G A T C C
SEQ. ID. NO. 2	T G G C A T G G A C G C T T A T C G A G C A G C T
SEQ. ID. NO. 3	G T T A C C A C A T T G G G A G G A A C C A G T T
SEQ. ID. NO.1	T T T G T C T C T G A A A A G A C C T T T G A A A
SEQ. ID. NO. 2	T C A G G G T G G C A G C T A C A A G A A G A T T
SEQ. ID. NO. 3	T C C T T T C G T C T G C C A G G C C C G C C T C
SEQ. ID. NO.1	C A C T T T G C A C C G T C A G G A C C T G G A T
SEQ. ID. NO. 2	G G C T A C T A T G A C A G C A C C A A G G A T G
SEQ. ID. NO. 3	T G G C T C C T G G G C C T G G G C T T T A G T C
SEQ. ID. NO.1	T C T C A C C G T G G G C T A C A C G A C C G C T
SEQ. ID. NO. 2	A T C T T T C C T G G T C C A A A A C A G A T A A
SEQ. ID. NO. 3	T G G G C T A C G G T T C C A T G T T C A C C A A
SEQ. ID. NO.1	T T T G G G G C C A T G T T T G C A A A G A C C T
SEQ. ID. NO. 2	A T G G A T T G G A G G G T C C C C C C C A G C T
SEQ. ID. NO. 3	G A T T T G G T G G G T C C A C A C G G T C T T C

FIG. 1g.

SEQ. ID. NO.1 G G A G A G T C C A C G C C A T C T T C A A A A A
SEQ. ID. NO. 2 G A C C A G A C C C T G G T C A T C A A G A C A T
SEQ. ID. NO. 3 A C A A A G A A G G A A G A A A A G A A G G A G T

SEQ. ID. NO.1 T G T G A A A A T G A A G A A G A A G A T C A T C
SEQ. ID. NO. 2 T C C G C T T C C T G T C A C A G A A A C T C T T
SEQ. ID. NO. 3 G G A G G A A G A C T C T G G A A C C C T G G A A

SEQ. ID. NO.1 A A G G A C C A G A A A C T G C T T G T G A T C G
SEQ. ID. NO. 2 T A T C T C C G T C T C A G T T C T C T C C A G C
SEQ. ID. NO. 3 G C T G T A T G C C A C A G T G G G C C T G C T G

SEQ. ID. NO.1 T G G G G G G C A T G C T G C T G A T C G A C C T
SEQ. ID. NO. 2 C T G G G C A T T G T C C T A G C T G T T G T C T
SEQ. ID. NO. 3 G T G G G C A T G G A T G T C C T C A C T C T C G

SEQ. ID. NO.1 G T G T A T C C T G A T C T G C T G G C A G G C T
SEQ. ID. NO. 2 G T C T G T C C T T T A A C A T C T A C A A C T C
SEQ. ID. NO. 3 C C A T C T G G C A G A T C G T G G A C C C T C T

SEQ. ID. NO.1 G T G G A C C C C C T G C G A A G G A C A G T G G
SEQ. ID. NO. 2 A C A T G T C C G T T A T A T C C A G A A C T C A
SEQ. ID. NO. 3 G C A C C G G A C C A T T G A G A C A T T T G C C

SEQ. ID. NO.1 A G A A G T A C A G C A T G G A G C C G G A C C C
SEQ. ID. NO. 2 C A G C C C A A C C T G A A C A A C C T G A C T G
SEQ. ID. NO. 3 A A G G A G G A A C C T A A G G A A G A T A T T G

SEQ. ID. NO.1 A G C A G G A C G G G A T A T C T C C A T C C G C
SEQ. ID. NO. 2 C T G T G G G C T G C T C A C T G G C T T T A G C
SEQ. ID. NO. 3 A C G T C T C T A T T C T G C C C C A G C T G G A

SEQ. ID. NO.1 C C T C T C C T G G A G C A C T G T G A G A A C A
SEQ. ID. NO. 2 T G C T G T C T T C C C C C T G G G G C T C G A T
SEQ. ID. NO. 3 G C A T T G C A G C T C C A G G A A G A T G A A T

SEQ. ID. NO.1 C C C A T A T G A C C A T C T G G C T T G G C A T
SEQ. ID. NO. 2 G G T T A C C A C A T T G G G A G G A A C C A G T
SEQ. ID. NO. 3 A C A T G G C T T G G C A T T T T C T A T G G T T

FIG. 1h.

SEQ. ID. NO.1 C G T C T A T G C C T A C A A G G G A C T T C T C
SEQ. ID. NO. 2 T T C C T T T C G T C T G C C A G G C C C G C C T
SEQ. ID. NO. 3 A C A A G G G G C T G C T G C T G C T G C T G G G

SEQ. ID. NO.1 A T G T T G T T C G G T T G T T T C T T A G C T T
SEQ. ID. NO. 2 C T G G C T C C T G G G C C T G G G C T T T A G T
SEQ. ID. NO. 3 A A T C T T C C T T G C T T A T G A G A C C A A G

SEQ. ID. NO.1 G G G A G A C C C G C A A C G T C A G C A T C C C
SEQ. ID. NO. 2 C T G G G C T A C G G T T C C A T G T T C A C C A
SEQ. ID. NO. 3 A G T G T G T C C A C T G A G A A G A T C A A T G

SEQ. ID. NO.1 C G C A C T C A A C G A C A G C A A G T A C A T C
SEQ. ID. NO. 2 A G A T T T G G T G G G T C C A C A C G G T C T T
SEQ. ID. NO. 3 A T C A C C G G G C T G T G G G C A T G G C T A T

SEQ. ID. NO.1 G G G A T G A G T G T C T A C A A C G T G G G G A
SEQ. ID. NO. 2 C A C A A A G A A G G A A G A A A A G A A G G A G
SEQ. ID. NO. 3 C T A C A A T G T G G C A G T C C T G T G C C T C

SEQ. ID. NO.1 T C A T G T G C A T C A T C G G G G C C G C T G T
SEQ. ID. NO. 2 T G G A G G A A G A C T C T G G A A C C C T G G A
SEQ. ID. NO. 3 A T C A C T G C T C C T G T C A C C A T G A T T C

SEQ. ID. NO.1 C T C C T T C C T G A C C C G G G A C C A G C C C
SEQ. ID. NO. 2 A G C T G T A T G C C A C A G T G G G C C T G C T
SEQ. ID. NO. 3 T G T C C A G C C A G C A G G A T G C A G C C T T

SEQ. ID. NO.1 A A T G T G C A G T T C T G C A T C G T G G C T C
SEQ. ID. NO. 2 G G T G G G C A T G G A T G T C C T C A C T C T C
SEQ. ID. NO. 3 T G C C T T T G C C T C T C T T G C C A T A G T T

SEQ. ID. NO.1 T G G T C A T C A T C T T C T G C A G C A C C A T
SEQ. ID. NO. 2 G C C A T C T G G C A G A T C G T G G A C C C T C
SEQ. ID. NO. 3 T T C T C C T C C T A T A T C A C T C T T G T T G

SEQ. ID. NO.1 C A C C C T C T G C C T G G T A T T C G T G C C G
SEQ. ID. NO. 2 T G C A C C G G A C C A T T G A G A C A T T T G C
SEQ. ID. NO. 3 T G C T C T T T G T G C C C A A G A T G C G C A G

FIG. 1i.

SEQ. ID. NO.1 A A G C T C A T C A C C C T G A G A A C A A A C C
SEQ. ID. NO. 2 C A A G G A G G A A C C T A A G G A A G A T A T T
SEQ. ID. NO. 3 G C T G A T C A C C C G A G G G G A A T G G C A G

SEQ. ID. NO.1 C A G A T G C A G C A A C G C A G A A C A G G C G
SEQ. ID. NO. 2 G A C G T C T C T A T T C T G C C C C A G C T G G
SEQ. ID. NO. 3 T C G G A G G C G C A G G A C A C C A T G A A G A

SEQ. ID. NO.1 A T T C C A G T T C A C T C A G A A T C A G A A G
SEQ. ID. NO. 2 A G C A T T G C A G C T C C A G G A A G A T G A A
SEQ. ID. NO. 3 C A G G G T C A T C G A C C A A C A A C A A C G A

SEQ. ID. NO.1 A A A G A A G A T T C T A A A A C G T C C A C C T
SEQ. ID. NO. 2 T A C A T G G C T T G G C A T T T T C T A T G G T
SEQ. ID. NO. 3 G G A G G A G A A G T C C C G G C T G T T G G A G

SEQ. ID. NO.1 C G G T C A C C A G T G T G A A C C A A G C C A G
SEQ. ID. NO. 2 T A C A A G G G G C T G C T G C T G C T G C T G G
SEQ. ID. NO. 3 A A G G A G A A C C G T G A A C T G G A A A A G A

SEQ. ID. NO.1 C A C A T C C C G C C T G G A G G G C C T A C A G
SEQ. ID. NO. 2 G A A T C T T C C T T G C T T A T G A G A C C A A
SEQ. ID. NO. 3 T C A T T G C T G A G A A A G A G G A G C G T G T

SEQ. ID. NO.1 T C A G A A A A C C A T C G C C T G C G A A T G A
SEQ. ID. NO. 2 G A G T G T G T C C A C T G A G A A G A T C A A T
SEQ. ID. NO. 3 C T C T G A A C T G C G C C A T C A A C T C C A G

SEQ. ID. NO.1 A G A T C A C A G A G C T G G A T A A A G A C T T
SEQ. ID. NO. 2 G A T C A C C G G G C T G T G G G C A T G G C T A
SEQ. ID. NO. 3 T C T C G G C A G C A G C T C C G C T C C C C G G C

SEQ. ID. NO.1 G G A A G A G G T C A C C A T G C A G C T G C A G
SEQ. ID. NO. 2 T C T A C A A T G T G G C A G T C C T G T G C C T
SEQ. ID. NO. 3 G C C A C C C A C C G A C A C C C C C A G A A C C

SEQ. ID. NO.1 G A C A C A C C A G A A A A G A C C A C C T A C A
SEQ. ID. NO. 2 C A T C A C T G C T C C T G T C A C C A T G A T T
SEQ. ID. NO. 3 C T C T G G G G G C C T G C C C A G G G G A C C C

FIG. 1j.

SEQ. ID. NO.1	T T A A A C A G A A C C A C T A C C A A G A G C T
SEQ. ID. NO. 2	C T G T C C A G C C A G C A G G A T G C A G C C T
SEQ. ID. NO. 3	C C T G A G C C C C C C G A C C G G C T T A G C T
SEQ. ID. NO.1	C A A T G A C A T C C T C A A C C T G G G A A A C
SEQ. ID. NO. 2	T T G C C T T T G C C T C T C T T G C C A T A G T
SEQ. ID. NO. 3	G T G A T G G G A G T C G A G T G C A T T T G C T
SEQ. ID. NO.1	T T C A C T G A G A G C A C A G A T G G A G G A A
SEQ. ID. NO. 2	T T T C T C C T C C T A T A T C A C T C T T G T T
SEQ. ID. NO. 3	T T A T A A G T G A G G G T A G G G T G A G G G A
SEQ. ID. NO.1	A G G C C A T T T T A A A A A A T C A C C T C G A
SEQ. ID. NO. 2	G T G C T C T T T G T G C C C A A G A T G C G C A
SEQ. ID. NO. 3	G G A C A G G C C A G T A G G G G G A G G G A A A
SEQ. ID. NO.1	T C A A A A T C C C C A G C T A C A G T G G A A C
SEQ. ID. NO. 2	G G C T G A T C A C C C G A G G G G A A T G G C A
SEQ. ID. NO. 3	G G G A G A G G G G A A G G G C A G G G G A C T C
SEQ. ID. NO.1	A C A A C A G A G C C C T C T C G A A C A T G C A
SEQ. ID. NO. 2	G T C G G A G G C G C A G G A C A C C A T G A A G
SEQ. ID. NO. 3	A G G A A G C A G G G G G T C C C C A T C C C C A
SEQ. ID. NO.1	A A G A T C C T A T A G A A G A T A T A A A C T C
SEQ. ID. NO. 2	A C A G G G T C A T C G A C C A A C A A C A A C G
SEQ. ID. NO. 3	G C T G G G A A G A A C A T G C T A T C C A A T C
SEQ. ID. NO.1	T C C A G A A C A C A T C C A G C G T C G G C T G
SEQ. ID. NO. 2	A G G A G G A G A A G T C C C G G C T G T T G G A
SEQ. ID. NO. 3	T C A T C T C T T G T A A A T A C A T G T C C C C
SEQ. ID. NO.1	T C C C T C C A G C T C C C C A T C C T C C A C C
SEQ. ID. NO. 2	G A A G G A G A A C C G T G A A C T G G A A A A G
SEQ. ID. NO. 3	C T G T G A G T T C T G G G C T G A T T T G G G T
SEQ. ID. NO.1	A C G C C T A C C T C C C A T C C A T C G G A G G
SEQ. ID. NO. 2	A T C A T T G C T G A G A A A G A G G A G C G T G
SEQ. ID. NO. 3	C T C T C A T A C C T C T G G G A A A C A G A C C

FIG. 1k.

SEQ. ID. NO.1 C G T G G A C G C C A G C T G T G T C A G C C C C
SEQ. ID. NO. 2 T C T C T G A A C T G C G C C A T C A G C T C C A
SEQ. ID. NO. 3 T T T T T C T C T C T T A C T G C T T C A T G T A

SEQ. ID. NO.1 T G C G T C A G C C C C A C C G C C A G C C C C C
SEQ. ID. NO. 2 G T C T C G G C A G C A G C T C C G C T C C C G G
SEQ. ID. NO. 3 A T T T T G T A T C A C C T C T T C A C A A T T T

SEQ. ID. NO.1 G C C A C A G A C A T G T G C C A C C C T C C T T
SEQ. ID. NO. 2 C G C C A C C C A C C G A C A C C C C C A G A A C
SEQ. ID. NO. 3 A G T T C G T A C C T G G C T T G A A G C T G C T

SEQ. ID. NO.1 C C G A G T C A T G G T C T C G G G C C T G
SEQ. ID. NO. 2 C C T C T G G G G G C C T G C C C A G G G G A C C
SEQ. ID. NO. 3 C A C T G C T C A C A C G C T G C C T C C T C A G

SEQ. ID. NO.1
SEQ. ID. NO. 2 C C C T G A G C C C C C C G A C C G G C T T A G C
SEQ. ID. NO. 3 C A G C C T C A C T G C A T C T T T C T C T T C C

SEQ. ID. NO.1
SEQ. ID. NO. 2 T G T G A T G G G A G T C G A G T G C A T T T G C
SEQ. ID. NO. 3 C A T G C A A C A C C C T C T T C T A G T T A C C

SEQ. ID. NO.1
SEQ. ID. NO. 2 T T T A T A A G T G A G G G T A G G G T G A G G G
SEQ. ID. NO. 3 A C G G C A A C C C C T

SEQ. ID. NO.1
SEQ. ID. NO. 2 A G G A C A G G C C A G T A G G G G G A G G G A A
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 A G G G A G A G G G G A A G G G C A G G G G A C T
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 C A G G A A G C A G G G G G T C C C C A T C C C C
SEQ. ID. NO. 3

FIG. 1L.

SEQ. ID. NO.1
SEQ. ID. NO. 2 A G C T G G G A A G A A C A T G C T A T C C A A T
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 C T C A T C T C T T G T A A A T A C A T G T C C C
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 C C T G T G A G T T C T G G G C T G A T T T G G G
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 T C T C T C A T A C C T C T G G G A A A C A G A C
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 C T T T T T C T C T C T T A C T G C T T C A T G T
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 A A T T T T G T A T C A C C T C T T C A C A A T T
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 T A G T T C G T A C C T G G C T T G A A G C T G C
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 T C A C T G C T C A C A C G C T G C C T C C T C A
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 G C A G C C T C A C T G C A T C T T T C T C T T C
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 C C A T G C A A C A C C C T C T T C T A G T T A C
SEQ. ID. NO. 3

FIG. 1m.

SEQ. ID. NO.1
SEQ. ID. NO. 2 C A C G G C A A C C C C T G C A G C T C C T C T G
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 C C T T T G T G C T C T G T T C C T G T C C A G C
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 A G G G G T C T C C C A A C A A G T G C T C T T T
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 C C A C C C C A A A G G G G C C T C T C C T T T T
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 C T C C A C T G T C A T A A T C T C T T T C C A T
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 C T T A C T T G C C C T T C T A T A C T T T C T C
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 A C A T G T G G C T C C C C C T G A A T T T T G C
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 T T C C T T T G G G G A G C T C A T T C T T T C G
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 C C A A G G T C A C A T G C T C C C T T G C C T C
SEQ. ID. NO. 3

SEQ. ID. NO.1
SEQ. ID. NO. 2 T G G C T C C G T G C A
SEQ. ID. NO. 3

FIG. 1n.

ClustalW Formatted Alignments

SEQ. ID. NO. 4	M A S P R S S G Q P G P X P P P P P P A R L L L
SEQ. ID. NO. 5	M L L L L L V P L F L R P L G A G G A Q T P N A T
SEQ. ID. NO. 6	M G P G G P C T P V G W P L P L L L V M A A G V A
SEQ. ID. NO. 7	M L L L L L L A P L F L R P P G A G G A Q T P N A
SEQ. ID. NO. 8	M G P G A P F A R V G W P L P L L V V M A A G V A

SEQ. ID. NO. 4	L L L L P L L L P L A P G A W G W A R G A P R P P
SEQ. ID. NO. 5	S E G C Q I I H P P W E G G I R Y R G L T R D Q V
SEQ. ID. NO. 6	P V W A S H S P H L P R P H P R V P P H P S S E R
SEQ. ID. NO. 7	T S E G C Q I I H P P W E G G I R Y R G L T R D Q
SEQ. ID. NO. 8	P V W A S H S P H L P R P H S R V P P H P S S E R

SEQ. ID. NO. 4	P S S P - P L S I M G L M P L T K E V A K G S I G
SEQ. ID. NO. 5	K A I N F L P V D Y E I E Y V C R G E R E V V G P
SEQ. ID. NO. 6	R A V Y I G A L F P M S G G W P G G Q A C Q P A V
SEQ. ID. NO. 7	V K A I N F L P V D Y E I E Y V C R G E R E V V G
SEQ. ID. NO. 8	R A V Y I G A L F P M S G G W P G G Q A C Q P A V

SEQ. ID. NO. 4	R G V L P A V E L A I E Q I R N E - S L L R P Y F
SEQ. ID. NO. 5	K V R K C L A N G S W T D M D T P S R C V R I C S
SEQ. ID. NO. 6	E M A L E D V N S R R D I L P D Y E L K L I H H D
SEQ. ID. NO. 7	P K V R K C L A N G S W T D M D T P S R C V R I C
SEQ. ID. NO. 8	E M A L E D V N S R R D I L P D Y E L K L I H H D

SEQ. ID. NO. 4	L D L R L Y D T E C D N A K G L K A F Y D A I K Y
SEQ. ID. NO. 5	K S Y L T L E N G K V F L T G G D L P A L D G A R
SEQ. ID. NO. 6	S K C D P G Q A T K Y L Y E L L Y N D P I K I I L
SEQ. ID. NO. 7	S K S Y L T L E N G K V F L T G G D L P A L D G A
SEQ. ID. NO. 8	S K C D P G Q A T K Y L Y E L L Y N D P I K I I L

SEQ. ID. NO. 4	G P N H L M V F G G V C P S V T S I I A E S L Q G
SEQ. ID. NO. 5	V E F R C D P D F H L V G S S R S V C S Q G Q W S
SEQ. ID. NO. 6	M P G C S S V S T L V A E A A R M W N L I V L S Y
SEQ. ID. NO. 7	R V D F R C D P D F H L V G S S R S I C S Q G Q W
SEQ. ID. NO. 8	M P G C S S V S T L V A E A A R M W N L I V L S Y

SEQ. ID. NO. 4	W N L V Q L S F A A T T P V L A D K K K Y P Y F F
SEQ. ID. NO. 5	T P K P H C Q V N R T P H S E R R A V Y I G A L F
SEQ. ID. NO. 6	G S S S P A L S N R Q R F P T F F R T H P S A T L
SEQ. ID. NO. 7	S T P K P H C Q V N R T P H S E R R A V Y I G A L
SEQ. ID. NO. 8	G S S S P A L S N R Q R F P T F F R T H P S A T L

FIG. 2a.

SEQ. ID. NO. 4	R T V P S D N A V N P A I L K L L K H Y Q W K R V
SEQ. ID. NO. 5	P M S G G W P G G Q A C Q P A V E M A L E D V N S
SEQ. ID. NO. 6	H N P T R V K L F E K W G W K K I A T I Q Q T T E
SEQ. ID. NO. 7	F P M S G G W P G G Q A C Q P A V E M A L E D V N
SEQ. ID. NO. 8	H N P T R V K L F E K W G W K K I A T I Q Q T T E

SEQ. ID. NO. 4	G T L T Q D V Q R F S E V R N D L T G V L Y G E D
SEQ. ID. NO. 5	R R D I L P D Y E L K L I H H D S K C D P G Q A T
SEQ. ID. NO. 6	V F T S T L D D L E E R V K E A G I E I T F R Q S
SEQ. ID. NO. 7	S R R D I L P D Y E L K L I H H D S K C D P G Q A
SEQ. ID. NO. 8	V F T S T L D D L E E R V K E A G I E I T F R Q S

SEQ. ID. NO. 4	I E I S D T E S F S N D P C T S V K K L K G N D V
SEQ. ID. NO. 5	K Y L Y E L L Y N D P I K I I L M P G C S S V S T
SEQ. ID. NO. 6	F F S D P A V P V K N L K R Q D A R I I V G L F Y
SEQ. ID. NO. 7	T K Y L Y E L L Y N D P I K I I L M P G C S S V S
SEQ. ID. NO. 8	F F S D P A V P V K N L K R Q D A R I I V G L F Y

SEQ. ID. NO. 4	R I I L G Q F D Q N M A A K V F C C A Y E E N M Y
SEQ. ID. NO. 5	L V A E A A R M W N L I V L S Y G S S S P A L S N
SEQ. ID. NO. 6	E T E A R K V F C E V Y K E R L F G K K Y V W F L
SEQ. ID. NO. 7	T L V A E A A R M W N L I V L S Y G S S S P A L S
SEQ. ID. NO. 8	E T E A R K V F C E V Y K E R L F G K K Y V W F L

SEQ. ID. NO. 4	G S K Y Q W I I P G W Y E P S W W E Q V H T E A N
SEQ. ID. NO. 5	R Q R F P T F F R T H P S A T L H N P T R V K L F
SEQ. ID. NO. 6	I G W Y A D N W F K T Y D P S I N C T V E E M T E
SEQ. ID. NO. 7	N R Q R F P T F F R T H P S A T L H N P T R V K L
SEQ. ID. NO. 8	I G W Y A D N W F K I Y D P S I N C T V D E M T E

SEQ. ID. NO. 4	S S R C L R K N L L A A M E G Y I G V D F E P L S
SEQ. ID. NO. 5	E K W G W K K I A T I Q Q T T E V F T S T L D D L
SEQ. ID. NO. 6	A V E G H I T T E I V M L N P A N T R S I S N M T
SEQ. ID. NO. 7	F E K W G W K K I A T I Q Q T T E V F T S T L D D
SEQ. ID. NO. 8	A V E G H I T T E I V M L N P A N T R S I S N M T

SEQ. ID. NO. 4	S K Q I K T I S G K T P Q Q Y E R E Y N N K R S G
SEQ. ID. NO. 5	E E R V K E A G I E I T F R Q S F F S D P A V P V
SEQ. ID. NO. 6	S Q E F V E K L T K R L K R H P E E T G G F Q E A
SEQ. ID. NO. 7	L E E R V K E A G I E I T F R Q S F F S D P A V P
SEQ. ID. NO. 8	S Q E F V E K L T K R L K R H P E E T G G F Q E A

FIG. 2b.

SEQ. ID. NO. 4 V G P S K F H G Y A Y D G I W V I A K T L Q R A M
SEQ. ID. NO. 5 K N L K R Q D A R I I V G L F Y E T E A R K V F C
SEQ. ID. NO. 6 P L A Y D A I W A L A L A L N K T S G G G G R S G
SEQ. ID. NO. 7 V K N L K R Q D A R I I V G L F Y E T E A R K V F
SEQ. ID. NO. 8 P L A Y D A I W A L A L A L N K T S G G G G R S G

SEQ. ID. NO. 4 E T L H A S S R H Q R I Q D F N Y T D H T L G R I
SEQ. ID. NO. 5 E V Y K E R L F G K K Y V W F L I G W Y A D N W F
SEQ. ID. NO. 6 V R L E D F N Y N N Q T I T D Q I Y R A M N S S S
SEQ. ID. NO. 7 C E V Y K E R L F G K K Y V W F L I G W Y A D N W
SEQ. ID. NO. 8 V R L E D F N Y N N Q T I T D Q I Y R A M N S S S

SEQ. ID. NO. 4 I L N A M N E T N F F G V T G Q V V F R N G E R M
SEQ. ID. NO. 5 K T Y D P S I N C T V E E M T E A V E G H I T T E
SEQ. ID. NO. 6 F E G V S G H V V F D A S G S R M A W T L I E Q L
SEQ. ID. NO. 7 F K I Y D P S I N C T V D E M T E A V E G H I T T
SEQ. ID. NO. 8 F E G V S G H V V F D A S G S R M A W T L I E Q L

SEQ. ID. NO. 4 G T I K F T Q F Q D S R E V K V G E Y N A V A D T
SEQ. ID. NO. 5 I V M L N P A N T R S I S N M T S Q E F V E K L T
SEQ. ID. NO. 6 Q G G S Y K K I G Y Y D S T K D D L S W S K T D K
SEQ. ID. NO. 7 E I V M L N P A N T R S I S N M T S Q E F V E K L
SEQ. ID. NO. 8 Q G G S Y K K I G Y Y D S T K D D L S W S K T D K

SEQ. ID. NO. 4 L E I I N D T I R F Q G S E P P K D K T I I L E Q
SEQ. ID. NO. 5 K R L K R H P E E T G G F Q E A P L A Y D A I W A
SEQ. ID. NO. 6 W I G G S P P A D Q I L V I K T F R F L S Q K L F
SEQ. ID. NO. 7 T K R L K R H P E E T G G F Q E A P L A Y D A I W
SEQ. ID. NO. 8 W I G G S P P A D Q T L V I K T F R F L S Q K L F

SEQ. ID. NO. 4 L R K I S L P L Y S I L S A L T I L G M I M A S A
SEQ. ID. NO. 5 L A L A L N K T S G G G G R S G V R L E D F N Y N
SEQ. ID. NO. 6 I S V S V L S S L G I V L A V V C L S F N I Y N S
SEQ. ID. NO. 7 A L A L A L N K T S G G G G R S G V R L E D F N Y
SEQ. ID. NO. 8 I S V S V L S S L G I V L A V V C L S F N I Y N S

SEQ. ID. NO. 4 F L F F N I K N R N Q K L I K M S S P Y M N N L I
SEQ. ID. NO. 5 N Q T I T D Q I Y R A M N S S S F E G V S G H V V
SEQ. ID. NO. 6 H V R Y I Q N S Q P N L N N L T A V G C S L A L A
SEQ. ID. NO. 7 N N Q T I T D Q I Y R A M N S S S F E G V S G H V
SEQ. ID. NO. 8 H V R Y I Q N S Q P N L N N L T A V G C S L A L A

FIG. 2c.

SEQ. ID. NO. 4 I L G G M L S Y A S I F L F G L D G S F V S E K T
SEQ. ID. NO. 5 F D A S G S R M A W T L I E Q L Q G G S Y K K I G
SEQ. ID. NO. 6 A V F P L G L D G Y H I G R S Q F P F V C Q A R L
SEQ. ID. NO. 7 V F D A S G S R M A W T L I E Q L Q G G S Y K K I
SEQ. ID. NO. 8 A V F P L G L D G Y H I G R N Q F P F V C Q A R L

SEQ. ID. NO. 4 F E T L C T V R T W I L T V G Y T T A F G A M F A
SEQ. ID. NO. 5 Y Y D S T K D D L S W S K T D K W I G G S P P A D
SEQ. ID. NO. 6 W L L G L G F S L G Y G S M F T K I W W V H T V F
SEQ. ID. NO. 7 G Y Y D S T K D D L S W S K T D K W I G G S P P A
SEQ. ID. NO. 8 W L L G L G F S L G Y G S M F T K I W W V H T V F

SEQ. ID. NO. 4 K T W R V H A I F K N V K M K K K I I K D Q K L L
SEQ. ID. NO. 5 Q I L V I K T F R F L S Q K L F I S V S V L S S L
SEQ. ID. NO. 6 T K K E E K K E W R K T L E P W K L Y A T V G L L
SEQ. ID. NO. 7 D Q T L V I K T F R F L S Q K L F I S V S V L S S
SEQ. ID. NO. 8 T K K E E K K E W R K T L E P W K L Y A T V G L L

SEQ. ID. NO. 4 V I V G G M L L I D L C I L I C W Q A V D P L R R
SEQ. ID. NO. 5 G I V L A V V C L S F N I Y N S H V R Y I Q N S Q
SEQ. ID. NO. 6 V G M D V L T L A I W Q I V D P L H R T I E T F A
SEQ. ID. NO. 7 L G I V L A V V C L S F N I Y N S H V R Y I Q N S
SEQ. ID. NO. 8 V G M D V L T L A I W Q I V D P L H R T I E T F A

SEQ. ID. NO. 4 T V E K Y S M E P D P A G R D I S I R P L L E H C
SEQ. ID. NO. 5 P N L N N L T A V G C S L A L A A V F P L G L D G
SEQ. ID. NO. 6 K E E P K E D I D V S I L P Q L E H C S S K K M N
SEQ. ID. NO. 7 Q P N L N N L T A V G C S L A L A A V F P L G L D
SEQ. ID. NO. 8 K E E P K E D I D V S I L P Q L E H C S S R K M N

SEQ. ID. NO. 4 E N T H M T I W L G I V Y A Y K G L L M L F G C F
SEQ. ID. NO. 5 Y H I G R S Q F P F V C Q A R L W L L G L G F S L
SEQ. ID. NO. 6 T W L G I F Y G Y K G L L L L L G I F L A Y E T K
SEQ. ID. NO. 7 G Y H I G R N Q F P F V C Q A R L W L L G L G F S
SEQ. ID. NO. 8 T W L G I F Y G Y K G L L L L L G I F L A Y E T K

SEQ. ID. NO. 4 L A W E T R N V S I P A L N D S K Y I G M S V Y N
SEQ. ID. NO. 5 G Y G S M F T K I W W V H T V F T K K E E K K E W
SEQ. ID. NO. 6 S V S T E K I N D H R A V G M A I Y N V A V L C L
SEQ. ID. NO. 7 L G Y G S M F T K I W W V H T V F T K K E E K K E
SEQ. ID. NO. 8 S V S T E K I N D H R A V G M A I Y N V A V L C L

FIG. 2d.

SEQ. ID. NO. 4 V G I M C I I G A A V S F L T R D Q P N V Q F C I
SEQ. ID. NO. 5 R K T L E P W K L Y A T V G L L V G M D V L T L A
SEQ. ID. NO. 6 I T A P V T M I L S S Q Q D A A F A F A S L A I V
SEQ. ID. NO. 7 W R K T L E P W K L Y A T V G L L V G M D V L T L
SEQ. ID. NO. 8 I T A P V T M I L S S Q Q D A A F A F A S L A I V

SEQ. ID. NO. 4 V A L V I I F C S T I T L C L V F V P K L I T L R
SEQ. ID. NO. 5 I W Q I V D P L H R T I E T F A K E E P K E D I D
SEQ. ID. NO. 6 F S S Y I T L V V L F V P K M R R L I T R G E W Q
SEQ. ID. NO. 7 A I W Q I V D P L H R T I E T F A K E E P K E D I
SEQ. ID. NO. 8 F S S Y I T L V V L F V P K M R R L I T R G E W Q

SEQ. ID. NO. 4 T N P D A A T Q N R R F Q F T Q N Q K K E D S K T
SEQ. ID. NO. 5 V S I L P Q L E H C S S K K M N T W L G I F Y G Y
SEQ. ID. NO. 6 S E T Q D T M K T G S S T N N N E E E K S R L L E
SEQ. ID. NO. 7 D V S I L P Q L E H C S S R K M N T W L G I F Y G
SEQ. ID. NO. 8 S E A Q D T M K T G S S T N N N E E E K S R L L E

SEQ. ID. NO. 4 S T S V T S V N Q A S T S R L E G L Q S E N H R L
SEQ. ID. NO. 5 K G L L L L L G I F L A Y E T K S V S T E K I N D
SEQ. ID. NO. 6 K E N R E L E K I I A E K E E R V S E L R H Q L Q
SEQ. ID. NO. 7 Y K G L L L L L G I F L A Y E T K S V S T E K I N
SEQ. ID. NO. 8 K E N R E L E K I I A E K E E R V S E L R H Q L Q

SEQ. ID. NO. 4 R M K I T E L D K D L E E V T M Q L Q D T P E K T
SEQ. ID. NO. 5 H R A V G M A I Y N V A V L C L I T A P V T M I L
SEQ. ID. NO. 6 S R Q Q L R S R R H P P T P P D P S G G L P R G P
SEQ. ID. NO. 7 D H R A V G M A I Y N V A V L C L I T A P V T M I
SEQ. ID. NO. 8 S R Q Q L R S R R H P P T P P E P S G G L P R G P

SEQ. ID. NO. 4 T Y I K Q N H Y Q E L N D I L N L G N F T E S T D
SEQ. ID. NO. 5 S S Q Q D A A F A F A S L A I V F S S Y I T L V V
SEQ. ID. NO. 6 S E P P D R L S C D G S R V H L L Y K
SEQ. ID. NO. 7 L S S Q Q D A A F A F A S L A I V F S S Y I T L V
SEQ. ID. NO. 8 P E P P D R L S C D G S R V H L L Y K

SEQ. ID. NO. 4 G G K A I L K N H L D Q N P Q L Q W N T T E P S R
SEQ. ID. NO. 5 L F V P K M R R L I T R G E W Q S E T Q D T M K T
SEQ. ID. NO. 6
SEQ. ID. NO. 7 V L F V P K M R R L I T R G E W Q S E A Q D T M K
SEQ. ID. NO. 8

FIG. 2e.

SEQ. ID. NO. 4	T C K D P I E D I N S P E H I Q R R L S L Q L P I
SEQ. ID. NO. 5	G S S T N N N E E E K S R L L E K E N R E L E K I
SEQ. ID. NO. 6	
SEQ. ID. NO. 7	T G S S T N N N E E E K S R L L E K E N R E L E K
SEQ. ID. NO. 8	

SEQ. ID. NO. 4	L H H A Y L P S I G G V D A S C V S P C V S P T A
SEQ. ID. NO. 5	I A E K E E R V S E L R H Q L Q S R Q Q L R S R R
SEQ. ID. NO. 6	
SEQ. ID. NO. 7	I I A E K E E R V S E L R H Q L Q S R Q Q L R S R
SEQ. ID. NO. 8	

SEQ. ID. NO. 4	S P R H R H V P P S F R V M V S G L
SEQ. ID. NO. 5	H P P T P P D P S G G L P R G P S E P P D R L S C
SEQ. ID. NO. 6	
SEQ. ID. NO. 7	R H P P T P P E P S G G L P R G P P E P P D R L S
SEQ. ID. NO. 8	

SEQ. ID. NO. 4	
SEQ. ID. NO. 5	D G S R V H L L Y K
SEQ. ID. NO. 6	
SEQ. ID. NO. 7	C D G S R V H L L Y K
SEQ. ID. NO. 8	

FIG. 2f.

ATG GCA TTT TAT AGC
Met Ala Phe Tyr Ser>

TGC TGC TGG GTC CTC TTG GCA CTC ACC TGG CAC ACC TCT GCC TAC GGG CCA GAC
Cys Cys Trp Val Leu Leu Ala Leu Thr Trp His Thr Ser Ala Tyr Gly Pro Asp>

CAG CGA GCC CAA AAG AAG GGG GAC ATT ATC CTT GGG GGG CTC TTT CCT ATT CAT
Gln Arg Ala Gln Lys Lys Gly Asp Ile Ile Leu Gly Gly Leu Phe Pro Ile His>

TTT GGA GTA GCA GCT AAA GAT CAA GAT CTC AAA TCA AGG CCG GAG TCT GTG GAA
Phe Gly Val Ala Ala Lys Asp Gln Asp Leu Lys Ser Arg Pro Glu Ser Val Glu>

TGT ATC AGG TAT AAT TTC CGT GGG TTT CGC TGG TTA CAG GCT ATG ATA TTT GCC
Cys Ile Arg Tyr Asn Phe Arg Gly Phe Arg Trp Leu Gln Ala Met Ile Phe Ala>

ATA GAG GAG ATA AAC AGC AGC CCA GCC CTT CTT CCC AAC TTG ACG CTG GGA TAC
Ile Glu Glu Ile Asn Ser Ser Pro Ala Leu Leu Pro Asn Leu Thr Leu Gly Tyr>

AGG ATA TTT GAC ACT TGC AAC ACC GTT TCT AAG GCC TTG GAA GCC ACC CTG AGT
Arg Ile Phe Asp Thr Cys Asn Thr Val Ser Lys Ala Leu Glu Ala Thr Leu Ser>

TTT GTT GCT CAA AAC AAA ATT GAT TCT TTG AAC CTT GAT GAG TTC TGC AAC TGC
Phe Val Ala Gln Asn Lys Ile Asp Ser Leu Asn Leu Asp Glu Phe Cys Asn Cys>

TCA GAG CAC ATT CCC TCT ACG ATT GCT GTG GTG GGA GCA ACT GGC TCA GGC GTC
Ser Glu His Ile Pro Ser Thr Ile Ala Val Val Gly Ala Thr Gly Ser Gly Val>

TCC ACG GCA GTG GCA AAT CTG CTG GGG CTC TTC TAC ATT CCC CAG GTC AGT TAT
Ser Thr Ala Val Ala Asn Leu Leu Gly Leu Phe Tyr Ile Pro Gln Val Ser Tyr>

GCC TCC TCC AGC AGA CTC CTC AGC AAC AAG AAT CAA TTC AAG TCT TTC CTC CGA
Ala Ser Ser Ser Arg Leu Leu Ser Asn Lys Asn Gln Phe Lys Ser Phe Leu Arg>

ACC ATC CCC AAT GAT GAG CAC CAG GCC ACT GCC ATG GCA GAC ATC ATC GAG TAT
Thr Ile Pro Asn Asp Glu His Gln Ala Thr Ala Met Ala Asp Ile Ile Glu Tyr>

TTC CGC TGG AAC TGG GTG GGC ACA ATT GCA GCT GAT GAC GAC TAT GGG CGG CCG
Phe Arg Trp Asn Trp Val Gly Thr Ile Ala Ala Asp Asp Asp Tyr Gly Arg Pro>

GGG ATT GAG AAA TTC CGA GAG GAA GCT GAG GAA AGG GAT ATC TGC ATC GAC TTC
Gly Ile Glu Lys Phe Arg Glu Glu Ala Glu Glu Arg Asp Ile Cys Ile Asp Phe>

AGT GAA CTC ATC TCC CAG TAC TCT GAT GAG GAA GAG ATC CAG CAT GTG GTA GAG
Ser Glu Leu Ile Ser Gln Tyr Ser Asp Glu Glu Glu Ile Gln His Val Val Glu>

GTG ATT CAA AAT TCC ACG GCC AAA GTC ATC GTG GTT TTC TCC AGT GGC CCA GAT
Val Ile Gln Asn Ser Thr Ala Lys Val Ile Val Val Phe Ser Ser Gly Pro Asp>

FIG. 3a.

CTT GAG CCC CTC ATC AAG GAG ATT GTC CGG CGC AAT ATC ACG GGC AAG ATC TGG
Leu Glu Pro Leu Ile Lys Glu Ile Val Arg Arg Asn Ile Thr Gly Lys Ile Trp>

CTG GCC AGC GAG GCC TGG GCC AGC TCC TCC CTG ATC GCC ATG CCT CAG TAC TTC
Leu Ala Ser Glu Ala Trp Ala Ser Ser Ser Leu Ile Ala Met Pro Gln Tyr Phe>

CAC GTG GTT GGC GGC ACC ATT GGA TTC GCT CTG AAG GCT GGG CAG ATC CCA GGC
His Val Val Gly Gly Thr Ile Gly Phe Ala Leu Lys Ala Gly Gln Ile Pro Gly>

TTC CGG GAA TTC CTG AAG AAG GTC CAT CCC AGG AAG TCT GTC CAC AAT GGT TTT
Phe Arg Glu Phe Leu Lys Lys Val His Pro Arg Lys Ser Val His Asn Gly Phe>

GCC AAG GAG TTT TGG GAA GAA ACA TTT AAC TGC CAC CTC CAA GAA GGT GCA AAA
Ala Lys Glu Phe Trp Glu Glu Thr Phe Asn Cys His Leu Gln Glu Gly Ala Lys>

GGA CCT TTA CCT GTG GAC ACC TTT CTG AGA GGT CAC GAA GAA AGT GGC GAC AGG
Gly Pro Leu Pro Val Asp Thr Phe Leu Arg Gly His Glu Glu Ser Gly Asp Arg>

TTT AGC AAC AGC TCG ACA GCC TTC CGA CCC CTC TGT ACA GGG GAT GAG AAC ATC
Phe Ser Asn Ser Ser Thr Ala Phe Arg Pro Leu Cys Thr Gly Asp Glu Asn Ile>

AGC AGT GTC GAG ACC CCT TAC ATA GAT TAC ACG CAT TTA CGG ATA TCC TAC AAT
Ser Ser Val Glu Thr Pro Tyr Ile Asp Tyr Thr His Leu Arg Ile Ser Tyr Asn>

GTG TAC TTA GCA GTC TAC TCC ATT GCC CAC GCC TTG CAA GAT ATA TAT ACC TGC
Val Tyr Leu Ala Val Tyr Ser Ile Ala His Ala Leu Gln Asp Ile Tyr Thr Cys>

TTA CCT GGG AGA GGG CTC TTC ACC AAT GGC TCC TGT GCA GAC ATC AAG AAA GTT
Leu Pro Gly Arg Gly Leu Phe Thr Asn Gly Ser Cys Ala Asp Ile Lys Lys Val>

GAG GCG TGG CAG GTC CTG AAG CAC CTA CGG CAT CTA AAC TTT ACA AAC AAT ATG
Glu Ala Trp Gln Val Leu Lys His Leu Arg His Leu Asn Phe Thr Asn Asn Met>

GGG GAG CAG GTG ACC TTT GAT GAG TGT GGT GAC CTG GTG GGG AAC TAT TCC ATC
Gly Glu Gln Val Thr Phe Asp Glu Cys Gly Asp Leu Val Gly Asn Tyr Ser Ile>

ATC AAC TGG CAC CTC TCC CCA GAG GAT GGC TCC ATC GTG TTT AAG GAA GTC GGG
Ile Asn Trp His Leu Ser Pro Glu Asp Gly Ser Ile Val Phe Lys Glu Val Gly>

TAT TAC AAC GTC TAT GCC AAG AAG GGA GAA AGA CTC TTC ATC AAC GAG GAG AAA
Tyr Tyr Asn Val Tyr Ala Lys Lys Gly Glu Arg Leu Phe Ile Asn Glu Glu Lys>

ATC CTG TGG AGT GGG TTC TCC AGG GAG GTG CCC TTC TCC AAC TGC AGC CGA GAC
Ile Leu Trp Ser Gly Phe Ser Arg Glu Val Pro Phe Ser Asn Cys Ser Arg Asp>

TGC CTG GCA GGG ACC AGG AAA GGG ATC ATT GAG GGG GAG CCC ACC TGC TGC TTT
Cys Leu Ala Gly Thr Arg Lys Gly Ile Ile Glu Gly Glu Pro Thr Cys Cys Phe>

GAG TGT GTG GAG TGT CCT GAT GGG GAG TAT AGT GAT GAG ACA GAT GCC AGT GCC
Glu Cys Val Glu Cys Pro Asp Gly Glu Tyr Ser Asp Glu Thr Asp Ala Ser Ala>

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FIG. 3b.

TGT AAC AAG TGC CCA GAT GAC TTC TGG TCC AAT GAG AAC CAC ACC TCC TGC ATT
Cys Asn Lys Cys Pro Asp Asp Phe Trp Ser Asn Glu Asn His Thr Ser Cys Ile>

GCC AAG GAG ATC GAG TTT CTG TCG TGG ACG GAG CCC TTT GGG ATC GCA CTC ACC
Ala Lys Glu Ile Glu Phe Leu Ser Trp Thr Glu Pro Phe Gly Ile Ala Leu Thr>

CTC TTT GCC GTG CTG GGC ATT TTC CTG ACA GCC TTT GTG CTG GGT GTG TTT ATC
Leu Phe Ala Val Leu Gly Ile Phe Leu Thr Ala Phe Val Leu Gly Val Phe Ile>

AAG TTC CGC AAC ACA CCC ATT GTC AAG GCC ACC AAC CGA GAG CTC TCC TAC CTC
Lys Phe Arg Asn Thr Pro Ile Val Lys Ala Thr Asn Arg Glu Leu Ser Tyr Leu>

CTC CTC TTC TCC CTG CTC TGC TGC TTC TCC AGC TCC CTG TTC TTC ATC GGG GAG
Leu Leu Phe Ser Leu Leu Cys Cys Phe Ser Ser Ser Leu Phe Phe Ile Gly Glu>

CCC CAG GAC TGG ACG TGC CGC CTG CGC CAG CCG GCC TTT GGC ATC AGC TTC GTG
Pro Gln Asp Trp Thr Cys Arg Leu Arg Gln Pro Ala Phe Gly Ile Ser Phe Val>

CTC TGC ATC TCA TGC ATC CTG GTG AAA ACC AAC CGT GTC CTC CTG GTG TTT GAG
Leu Cys Ile Ser Cys Ile Leu Val Lys Thr Asn Arg Val Leu Leu Val Phe Glu>

GCC AAG ATC CCC ACC AGC TTC CAC CGC AAG TGG TGG GGG CTC AAC CTG CAG TTC
Ala Lys Ile Pro Thr Ser Phe His Arg Lys Trp Trp Gly Leu Asn Leu Gln Phe>

CTG CTG GTT TTC CTC TGC ACC TTC ATG CAG ATT GTC ATC TGT GTG ATC TGG CTC
Leu Leu Val Phe Leu Cys Thr Phe Met Gln Ile Val Ile Cys Val Ile Trp Leu>

TAC ACC GCG CCC CCC TCA AGC TAC CGC AAC CAG GAG CTG GAG GAT GAG ATC ATC
Tyr Thr Ala Pro Pro Ser Ser Tyr Arg Asn Gln Glu Leu Glu Asp Glu Ile Ile>

TTC ATC ACG TGC CAC GAG GGC TCC CTC ATG GCC CTG GGC TTC CTG ATC GGC TAC
Phe Ile Thr Cys His Glu Gly Ser Leu Met Ala Leu Gly Phe Leu Ile Gly Tyr>

ACC TGC CTG CTG GCT GCC ATC TGC TTC TTC TTT GCC TTC AAG TCC CGG AAG CTG
Thr Cys Leu Leu Ala Ala Ile Cys Phe Phe Phe Ala Phe Lys Ser Arg Lys Leu>

CCG GAG AAC TTC AAT GAA GCC AAG TTC ATC ACC TTC AGC ATG CTC ATC TTC TTC
Pro Glu Asn Phe Asn Glu Ala Lys Phe Ile Thr Phe Ser Met Leu Ile Phe Phe>

ATC GTC TGG ATC TCC TTC ATT CCA GCC TAT GCC AGC ACC TAT GGC AAG TTT GTC
Ile Val Trp Ile Ser Phe Ile Pro Ala Tyr Ala Ser Thr Tyr Gly Lys Phe Val>

TCT GCC GTA GAG GTG ATT GCC ATC CTG GCA GCC AGC TTT GGC TTG CTG GCG TGC
Ser Ala Val Glu Val Ile Ala Ile Leu Ala Ala Ser Phe Gly Leu Leu Ala Cys>

ATC TTC TTC AAC AAG ATC TAC ATC ATT CTC TTC AAG CCA TCC CGC AAC ACC ATC
Ile Phe Phe Asn Lys Ile Tyr Ile Ile Leu Phe Lys Pro Ser Arg Asn Thr Ile>

GAG GAG GTG CGT TGC AGC ACC GCA GCT CAC GCT TTC AAG GTG GCT GCC CGG GCC
Glu Glu Val Arg Cys Ser Thr Ala Ala His Ala Phe Lys Val Ala Ala Arg Ala>

ACG CTG CGC CGC AGC AAC GTC TCC CGC AAG CGG TCC AGC AGC CTT GGA GGC TCC
Thr Leu Arg Arg Ser Asn Val Ser Arg Lys Arg Ser Ser Ser Leu Gly Gly Ser>

FIG. 3c.

ACG GGA TCC ACC CCC TCC TCC TCC ATC AGC AGC AAG AGC AAC AGC GAA GAC CCA
Thr Gly Ser Thr Pro Ser Ser Ser Ile Ser Ser Lys Ser Asn Ser Glu Asp Pro>

TTC CCA CAG CCC GAG AGG CAG AAG CAG CAG CAG CCG CTG GCC CTA ACC CAG CAA
Phe Pro Gln Pro Glu Arg Gln Lys Gln Gln Gln Pro Leu Ala Leu Thr Gln Gln>

GAG CAG CAG CAG CAG CCC CTG ACC CTC CCA CAG CAG CAA CGA TCT CAG CAG CAG
Glu Gln Gln Gln Gln Pro Leu Thr Leu Pro Gln Gln Gln Arg Ser Gln Gln Gln>

CCC AGA TGC AAG CAG AAG GTC ATC TTT GGC AGC GGC ACG GTC ACC TTC TCA CTG
Pro Arg Cys Lys Gln Lys Val Ile Phe Gly Ser Gly Thr Val Thr Phe Ser Leu>

AGC TTT GAT GAG CCT CAG AAG AAC GCC ATG GCC CAC GGG AAT TCT ACG CAC CAG
Ser Phe Asp Glu Pro Gln Lys Asn Ala Met Ala His Gly Asn Ser Thr His Gln>

AAC TCC CTG GAG GCC CAG AAA AGC AGC GAT ACG CTG ACC CGA CAC CAG CCA TTA
Asn Ser Leu Glu Ala Gln Lys Ser Ser Asp Thr Leu Thr Arg His Gln Pro Leu>

CTC CCG CTG CAG TGC GGG GAA ACG GAC TTA GAT CTG ACC GTC CAG GAA ACA GGT
Leu Pro Leu Gln Cys Gly Glu Thr Asp Leu Asp Leu Thr Val Gln Glu Thr Gly>

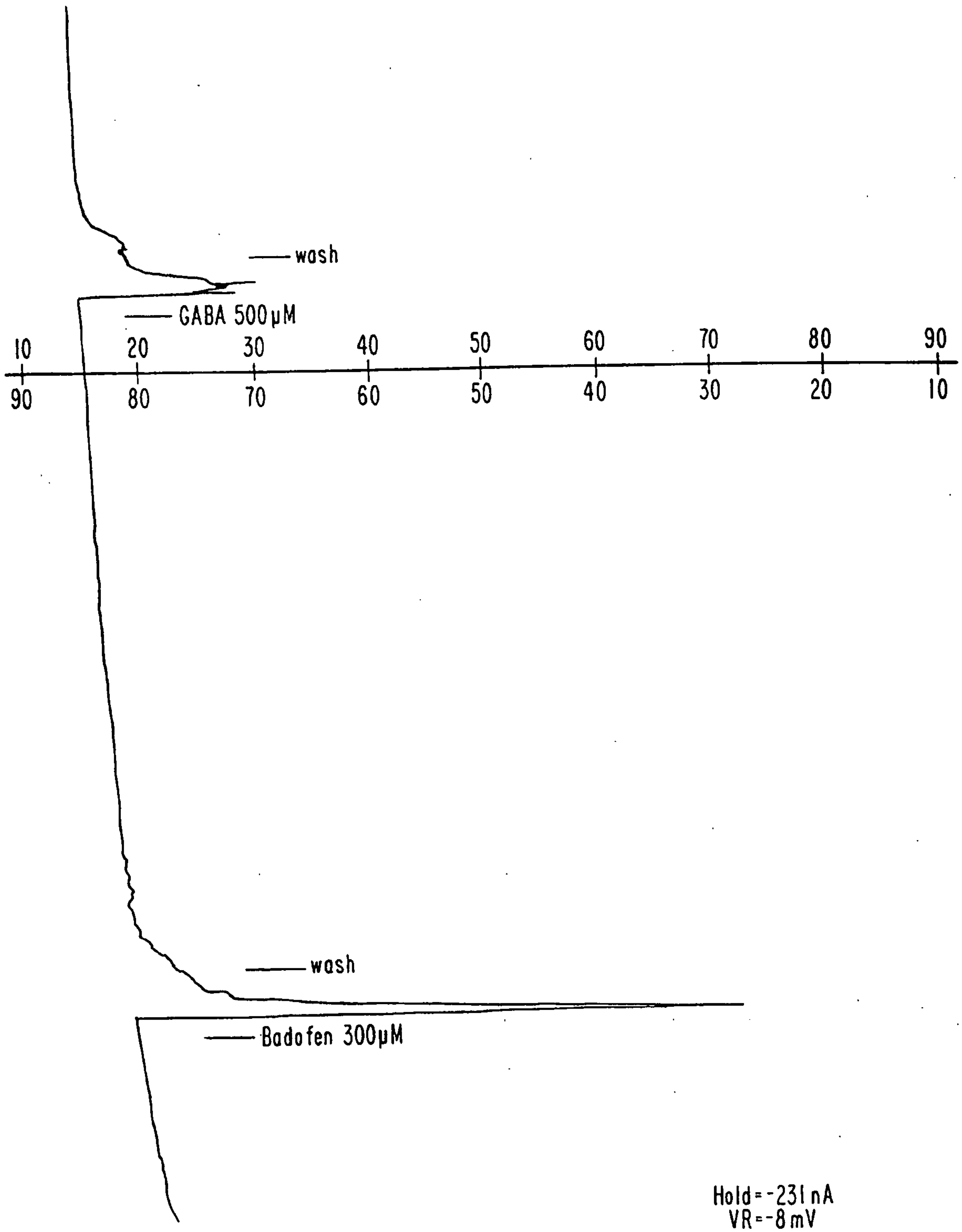
CTG CAA GGA CCT GTG GGT GGA GAC CAG CGG CCA GAG GTG GAG GAC CCT GAA GAG
Leu Gln Gly Pro Val Gly Gly Asp Gln Arg Pro Glu Val Glu Asp Pro Glu Glu>

TTG TCC CCA GCA CTT GTA GTG TCC AGT TCA CAG AGC TTT GTC ATC AGT GGT GGA
Leu Ser Pro Ala Leu Val Val Ser Ser Ser Gln Ser Phe Val Ile Ser Gly Gly>

GGC AGC ACT GTT ACA GAA AAC GTA GTG AAT TCA
Gly Ser Thr Val Thr Glu Asn Val Val Asn Ser>

FIG. 3d.

FIG. 4.



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Tyr Phe Leu Asp Leu Arg Leu Tyr Asp Thr Glu Cys Asp Asn Ala Lys
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Gly Leu Lys Ala Phe Tyr Asp Ala Ile Lys Tyr Gly Pro Asn His Leu
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Met Val Phe Gly Gly Val Cys Pro Ser Val Thr Ser Ile Ile Ala Glu
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Ser Leu Gln Gly Trp Asn Leu Val Gln Leu Ser Phe Ala Ala Thr Thr
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Pro Val Leu Ala Asp Lys Lys Lys Tyr Pro Tyr Phe Phe Arg Thr Val
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Pro Ser Asp Asn Ala Val Asn Pro Ala Ile Leu Lys Leu Leu Lys His
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Tyr Gln Trp Lys Arg Val Gly Thr Leu Thr Gln Asp Val Gln Arg Phe
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Ser Glu Val Arg Asn Asp Leu Thr Gly Val Leu Tyr Gly Glu Asp Ile
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Lys Lys Leu Lys Gly Asn Asp Val Arg Ile Ile Leu Gly Gln Phe Asp
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Gln Asn Met Ala Ala Lys Val Phe Cys Cys Ala Tyr Glu Glu Asn Met
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Tyr Gly Ser Lys Tyr Gln Trp Ile Ile Pro Gly Trp Tyr Glu Pro Ser
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Pro Leu Ser Ser Lys Gln Ile Lys Thr Ile Ser Gly Lys Thr Pro Gln
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Gln Tyr Glu Arg Glu Tyr Asn Asn Lys Arg Ser Gly Val Gly Pro Ser
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Lys Phe His Gly Tyr Ala Tyr Asp Gly Ile Trp Val Ile Ala Lys Thr
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Asn Ala Met Asn Glu Thr Asn Phe Phe Gly Val Thr Gly Gln Val Val
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Phe Arg Asn Gly Glu Arg Met Gly Thr Ile Lys Phe Thr Gln Phe Gln
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Asp Ser Arg Glu Val Lys Val Gly Glu Tyr Asn Ala Val Ala Asp Thr
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Leu Glu Ile Ile Asn Asp Thr Ile Arg Phe Gln Gly Ser Glu Pro Pro
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Lys Asp Lys Thr Ile Ile Leu Glu Gln Leu Arg Lys Ile Ser Leu Pro
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Leu Tyr Ser Ile Leu Ser Ala Leu Thr Ile Leu Gly Met Ile Met Ala
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Ser Ala Phe Leu Phe Phe Asn Ile Lys Asn Arg Asn Gln Lys Leu Ile
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Lys Met Ser Ser Pro Tyr Met Asn Asn Leu Ile Ile Leu Gly Gly Met
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Leu Ser Tyr Ala Ser Ile Phe Leu Phe Gly Leu Asp Gly Ser Phe Val
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Ser Glu Lys Thr Phe Glu Thr Leu Cys Thr Val Arg Thr Trp Ile Leu
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Thr Val Gly Tyr Thr Thr Ala Phe Gly Ala Met Phe Ala Lys Thr Trp
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Arg Val His Ala Ile Phe Lys Asn Val Lys Met Lys Lys Lys Ile Ile
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Lys Asp Gln Lys Leu Leu Val Ile Val Gly Gly Met Leu Leu Ile Asp
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Leu Cys Ile Leu Ile Cys Trp Gln Ala Val Asp Pro Leu Arg Arg Thr
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Val Glu Lys Tyr Ser Met Glu Pro Asp Pro Ala Gly Arg Asp Ile Ser
625                 630                 635                 640

Ile Arg Pro Leu Leu Glu His Cys Glu Asn Thr His Met Thr Ile Trp
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Leu Gly Ile Val Tyr Ala Tyr Lys Gly Leu Leu Met Leu Phe Gly Cys
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Phe Leu Ala Trp Glu Thr Arg Asn Val Ser Ile Pro Ala Leu Asn Asp
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Ser Lys Tyr Ile Gly Met Ser Val Tyr Asn Val Gly Ile Met Cys Ile
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Ile Gly Ala Ala Val Ser Phe Leu Thr Arg Asp Gln Pro Asn Val Gln
705 710 715 720

Phe Cys Ile Val Ala Leu Val Ile Ile Phe Cys Ser Thr Ile Thr Leu
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Cys Leu Val Phe Val Pro Lys Leu Ile Thr Leu Arg Thr Asn Pro Asp
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Ala Ala Thr Gln Asn Arg Arg Phe Gln Phe Thr Gln Asn Gln Lys Lys
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Glu Asp Ser Lys Thr Ser Thr Ser Val Thr Ser Val Asn Gln Ala Ser
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Thr Ser Arg Leu Glu Gly Leu Gln Ser Glu Asn His Arg Leu Arg Met
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Lys Ile Thr Glu Leu Asp Lys Asp Leu Glu Glu Val Thr Met Gln Leu
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Gln Asp Thr Pro Glu Lys Thr Thr Tyr Ile Lys Gln Asn His Tyr Gln
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Glu Leu Asn Asp Ile Leu Asn Leu Gly Asn Phe Thr Glu Ser Thr Asp
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Gly Gly Lys Ala Ile Leu Lys Asn His Leu Asp Gln Asn Pro Gln Leu
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Gln Trp Asn Thr Thr Glu Pro Ser Arg Thr Cys Lys Asp Pro Ile Glu
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Asp Ile Asn Ser Pro Glu His Ile Gln Arg Arg Leu Ser Leu Gln Leu
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Pro Ile Leu His His Ala Tyr Leu Pro Ser Ile Gly Gly Val Asp Ala
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His Pro Pro Trp Glu Gly Gly Ile Arg Tyr Arg Gly Leu Thr Arg Asp
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Gln Val Lys Ala Ile Asn Phe Leu Pro Val Asp Tyr Glu Ile Glu Tyr
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Val Cys Arg Gly Glu Arg Glu Val Val Gly Pro Lys Val Arg Lys Cys
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Leu Ala Asn Gly Ser Trp Thr Asp Met Asp Thr Pro Ser Arg Cys Val
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Arg Ile Cys Ser Lys Ser Tyr Leu Thr Leu Glu Asn Gly Lys Val Phe
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Leu Thr Gly Gly Asp Leu Pro Ala Leu Asp Gly Ala Arg Val Glu Phe
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Arg Cys Asp Pro Asp Phe His Leu Val Gly Ser Ser Arg Ser Val Cys
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Ser Gln Gly Gln Trp Ser Thr Pro Lys Pro His Cys Gln Val Asn Arg
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Thr Pro His Ser Glu Arg Arg Ala Val Tyr Ile Gly Ala Leu Phe Pro
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Met Ser Gly Gly Trp Pro Gly Gly Gln Ala Cys Gln Pro Ala Val Glu
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Met Ala Leu Glu Asp Val Asn Ser Arg Arg Asp Ile Leu Pro Asp Tyr
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Glu Leu Lys Leu Ile His His Asp Ser Lys Cys Asp Pro Gly Gln Ala
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Thr Lys Tyr Leu Tyr Glu Leu Leu Tyr Asn Asp Pro Ile Lys Ile Ile
225                 230                 235                 240

Leu Met Pro Gly Cys Ser Ser Val Ser Thr Leu Val Ala Glu Ala Ala
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Arg Met Trp Asn Leu Ile Val Leu Ser Tyr Gly Ser Ser Ser Pro Ala
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Leu Ser Asn Arg Gln Arg Phe Pro Thr Phe Phe Arg Thr His Pro Ser
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Ala Thr Leu His Asn Pro Thr Arg Val Lys Leu Phe Glu Lys Trp Gly
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Trp Lys Lys Ile Ala Thr Ile Gln Gln Thr Thr Glu Val Phe Thr Ser
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Leu Lys Arg Gln Asp Ala Arg Ile Ile Val Gly Leu Phe Tyr Glu Thr
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Glu Ala Arg Lys Val Phe Cys Glu Val Tyr Lys Glu Arg Leu Phe Gly
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Lys Lys Tyr Val Trp Phe Leu Ile Gly Trp Tyr Ala Asp Asn Trp Phe
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Lys Thr Tyr Asp Pro Ser Ile Asn Cys Thr Val Glu Glu Met Thr Glu
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Ala Ala Val Phe Pro Leu Gly Leu Asp Gly Tyr His Ile Gly Arg Ser
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Gln Phe Pro Phe Val Cys Gln Ala Arg Leu Trp Leu Leu Gly Leu Gly
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Phe Ser Leu Gly Tyr Gly Ser Met Phe Thr Lys Ile Trp Trp Val His
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Glu Pro Trp Lys Leu Tyr Ala Thr Val Gly Leu Leu Val Gly Met Asp
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Val Leu Thr Leu Ala Ile Trp Gln Ile Val Asp Pro Leu His Arg Thr
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Ile Glu Thr Phe Ala Lys Glu Glu Pro Lys Glu Asp Ile Asp Val Ser
            740                 745                 750

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Phe Ala Phe Ala Ser Leu Ala Ile Val Phe Ser Ser Tyr Ile Thr Leu
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Trp Gln Ser Glu Thr Gln Asp Thr Met Lys Thr Gly Ser Ser Thr Asn
865                 870                 875                 880

Asn Asn Glu Glu Glu Lys Ser Arg Leu Leu Glu Lys Glu Asn Arg Glu
                885                 890                 895

Leu Glu Lys Ile Ile Ala Glu Lys Glu Glu Arg Val Ser Glu Leu Arg
            900                 905                 910
```

```
His Gln Leu Gln Ser Arg Gln Gln Leu Arg Ser Arg Arg His Pro Pro
        915                 920                 925

Thr Pro Pro Asp Pro Ser Gly Gly Leu Pro Arg Gly Pro Ser Glu Pro
    930                 935                 940

Pro Asp Arg Leu Ser Cys Asp Gly Ser Arg Val His Leu Leu Tyr Lys
945                 950                 955                 960
```

<210> 6
<211> 844
<212> PRT
<213> Rat

<400> 6

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Met Gly Pro Gly Gly Pro Cys Thr Pro Val Gly Trp Pro Leu Pro Leu
1               5                   10                  15

Leu Leu Val Met Ala Ala Gly Val Ala Pro Val Trp Ala Ser His Ser
            20                  25                  30

Pro His Leu Pro Arg Pro His Pro Arg Val Pro Pro His Pro Ser Ser
        35                  40                  45

Glu Arg Arg Ala Val Tyr Ile Gly Ala Leu Phe Pro Met Ser Gly Gly
    50                  55                  60

Trp Pro Gly Gly Gln Ala Cys Gln Pro Ala Val Glu Met Ala Leu Glu
65                  70                  75                  80

Asp Val Asn Ser Arg Arg Asp Ile Leu Pro Asp Tyr Glu Leu Lys Leu
                85                  90                  95

Ile His His Asp Ser Lys Cys Asp Pro Gly Gln Ala Thr Lys Tyr Leu
            100                 105                 110

Tyr Glu Leu Leu Tyr Asn Asp Pro Ile Lys Ile Ile Leu Met Pro Gly
        115                 120                 125

Cys Ser Ser Val Ser Thr Leu Val Ala Glu Ala Ala Arg Met Trp Asn
    130                 135                 140

Leu Ile Val Leu Ser Tyr Gly Ser Ser Ser Pro Ala Leu Ser Asn Arg
145                 150                 155                 160

Gln Arg Phe Pro Thr Phe Phe Arg Thr His Pro Ser Ala Thr Leu His
                165                 170                 175

Asn Pro Thr Arg Val Lys Leu Phe Glu Lys Trp Gly Trp Lys Lys Ile
            180                 185                 190

Ala Thr Ile Gln Gln Thr Thr Glu Val Phe Thr Ser Thr Leu Asp Asp
        195                 200                 205
```

Leu Glu Glu Arg Val Lys Glu Ala Gly Ile Glu Ile Thr Phe Arg Gln
210 215 220

Ser Phe Phe Ser Asp Pro Ala Val Pro Val Lys Asn Leu Lys Arg Gln
225 230 235 240

Asp Ala Arg Ile Ile Val Gly Leu Phe Tyr Glu Thr Glu Ala Arg Lys
245 250 255

Val Phe Cys Glu Val Tyr Lys Glu Arg Leu Phe Gly Lys Lys Tyr Val
260 265 270

Trp Phe Leu Ile Gly Trp Tyr Ala Asp Asn Trp Phe Lys Thr Tyr Asp
275 280 285

Pro Ser Ile Asn Cys Thr Val Glu Glu Met Thr Glu Ala Val Glu Gly
290 295 300

His Ile Thr Thr Glu Ile Val Met Leu Asn Pro Ala Asn Thr Arg Ser
305 310 315 320

Ile Ser Asn Met Thr Ser Gln Glu Phe Val Glu Lys Leu Thr Lys Arg
325 330 335

Leu Lys Arg His Pro Glu Glu Thr Gly Gly Phe Gln Glu Ala Pro Leu
340 345 350

Ala Tyr Asp Ala Ile Trp Ala Leu Ala Leu Ala Leu Asn Lys Thr Ser
355 360 365

Gly Gly Gly Gly Arg Ser Gly Val Arg Leu Glu Asp Phe Asn Tyr Asn
370 375 380

Asn Gln Thr Ile Thr Asp Gln Ile Tyr Arg Ala Met Asn Ser Ser Ser
385 390 395 400

Phe Glu Gly Val Ser Gly His Val Val Phe Asp Ala Ser Gly Ser Arg
405 410 415

Met Ala Trp Thr Leu Ile Glu Gln Leu Gln Gly Gly Ser Tyr Lys Lys
420 425 430

Ile Gly Tyr Tyr Asp Ser Thr Lys Asp Asp Leu Ser Trp Ser Lys Thr
435 440 445

Asp Lys Trp Ile Gly Gly Ser Pro Pro Ala Asp Gln Ile Leu Val Ile
450 455 460

Lys Thr Phe Arg Phe Leu Ser Gln Lys Leu Phe Ile Ser Val Ser Val
465 470 475 480

Leu Ser Ser Leu Gly Ile Val Leu Ala Val Val Cys Leu Ser Phe Asn
485 490 495

Ile Tyr Asn Ser His Val Arg Tyr Ile Gln Asn Ser Gln Pro Asn Leu
500 505 510

Asn Asn Leu Thr Ala Val Gly Cys Ser Leu Ala Leu Ala Ala Val Phe
515 520 525

Pro Leu Gly Leu Asp Gly Tyr His Ile Gly Arg Ser Gln Phe Pro Phe
530 535 540

Val Cys Gln Ala Arg Leu Trp Leu Leu Gly Leu Gly Phe Ser Leu Gly
545 550 555 560

Tyr Gly Ser Met Phe Thr Lys Ile Trp Trp Val His Thr Val Phe Thr
565 570 575

Lys Lys Glu Glu Lys Lys Glu Trp Arg Lys Thr Leu Glu Pro Trp Lys
580 585 590

Leu Tyr Ala Thr Val Gly Leu Leu Val Gly Met Asp Val Leu Thr Leu
595 600 605

Ala Ile Trp Gln Ile Val Asp Pro Leu His Arg Thr Ile Glu Thr Phe
610 615 620

Ala Lys Glu Glu Pro Lys Glu Asp Ile Asp Val Ser Ile Leu Pro Gln
625 630 635 640

Leu Glu His Cys Ser Ser Lys Lys Met Asn Thr Trp Leu Gly Ile Phe
645 650 655

Tyr Gly Tyr Lys Gly Leu Leu Leu Leu Leu Gly Ile Phe Leu Ala Tyr
660 665 670

Glu Thr Lys Ser Val Ser Thr Glu Lys Ile Asn Asp His Arg Ala Val
675 680 685

Gly Met Ala Ile Tyr Asn Val Ala Val Leu Cys Leu Ile Thr Ala Pro
690 695 700

Val Thr Met Ile Leu Ser Ser Gln Gln Asp Ala Ala Phe Ala Phe Ala
705 710 715 720

Ser Leu Ala Ile Val Phe Ser Ser Tyr Ile Thr Leu Val Val Leu Phe
725 730 735

Val Pro Lys Met Arg Arg Leu Ile Thr Arg Gly Glu Trp Gln Ser Glu
740 745 750

Thr Gln Asp Thr Met Lys Thr Gly Ser Ser Thr Asn Asn Asn Glu Glu
755 760 765

Glu Lys Ser Arg Leu Leu Glu Lys Glu Asn Arg Glu Leu Glu Lys Ile
770 775 780

Ile Ala Glu Lys Glu Glu Arg Val Ser Glu Leu Arg His Gln Leu Gln
785 790 795 800

Ser Arg Gln Gln Leu Arg Ser Arg Arg His Pro Pro Thr Pro Pro Asp
805 810 815

```
Pro Ser Gly Gly Leu Pro Arg Gly Pro Ser Glu Pro Pro Asp Arg Leu
            820                 825                 830

Ser Cys Asp Gly Ser Arg Val His Leu Leu Tyr Lys
        835                 840



      <210> 7
      <211> 961
      <212> PRT
      <213> Human

      <400> 7

Met Leu Leu Leu Leu Leu Leu Ala Pro Leu Phe Leu Arg Pro Pro Gly
 1               5                  10                  15

Ala Gly Gly Ala Gln Thr Pro Asn Ala Thr Ser Glu Gly Cys Gln Ile
            20                  25                  30

Ile His Pro Pro Trp Glu Gly Gly Ile Arg Tyr Arg Gly Leu Thr Arg
        35                  40                  45

Asp Gln Val Lys Ala Ile Asn Phe Leu Pro Val Asp Tyr Glu Ile Glu
    50                  55                  60

Tyr Val Cys Arg Gly Glu Arg Glu Val Val Gly Pro Lys Val Arg Lys
65                  70                  75                  80

Cys Leu Ala Asn Gly Ser Trp Thr Asp Met Asp Thr Pro Ser Arg Cys
                85                  90                  95

Val Arg Ile Cys Ser Lys Ser Tyr Leu Thr Leu Glu Asn Gly Lys Val
            100                 105                 110

Phe Leu Thr Gly Gly Asp Leu Pro Ala Leu Asp Gly Ala Arg Val Asp
        115                 120                 125

Phe Arg Cys Asp Pro Asp Phe His Leu Val Gly Ser Ser Arg Ser Ile
    130                 135                 140

Cys Ser Gln Gly Gln Trp Ser Thr Pro Lys Pro His Cys Gln Val Asn
145                 150                 155                 160

Arg Thr Pro His Ser Glu Arg Arg Ala Val Tyr Ile Gly Ala Leu Phe
                165                 170                 175

Pro Met Ser Gly Gly Trp Pro Gly Gly Gln Ala Cys Gln Pro Ala Val
            180                 185                 190

Glu Met Ala Leu Glu Asp Val Asn Ser Arg Arg Asp Ile Leu Pro Asp
        195                 200                 205

Tyr Glu Leu Lys Leu Ile His His Asp Ser Lys Cys Asp Pro Gly Gln
    210                 215                 220
```

Ala Thr Lys Tyr Leu Tyr Glu Leu Leu Tyr Asn Asp Pro Ile Lys Ile
225 230 235 240

Ile Leu Met Pro Gly Cys Ser Ser Val Ser Thr Leu Val Ala Glu Ala
245 250 255

Ala Arg Met Trp Asn Leu Ile Val Leu Ser Tyr Gly Ser Ser Ser Pro
260 265 270

Ala Leu Ser Asn Arg Gln Arg Phe Pro Thr Phe Phe Arg Thr His Pro
275 280 285

Ser Ala Thr Leu His Asn Pro Thr Arg Val Lys Leu Phe Glu Lys Trp
290 295 300

Gly Trp Lys Lys Ile Ala Thr Ile Gln Gln Thr Thr Glu Val Phe Thr
305 310 315 320

Ser Thr Leu Asp Asp Leu Glu Glu Arg Val Lys Glu Ala Gly Ile Glu
325 330 335

Ile Thr Phe Arg Gln Ser Phe Phe Ser Asp Pro Ala Val Pro Val Lys
340 345 350

Asn Leu Lys Arg Gln Asp Ala Arg Ile Ile Val Gly Leu Phe Tyr Glu
355 360 365

Thr Glu Ala Arg Lys Val Phe Cys Glu Val Tyr Lys Glu Arg Leu Phe
370 375 380

Gly Lys Lys Tyr Val Trp Phe Leu Ile Gly Trp Tyr Ala Asp Asn Trp
385 390 395 400

Phe Lys Ile Tyr Asp Pro Ser Ile Asn Cys Thr Val Asp Glu Met Thr
405 410 415

Glu Ala Val Glu Gly His Ile Thr Thr Glu Ile Val Met Leu Asn Pro
420 425 430

Ala Asn Thr Arg Ser Ile Ser Asn Met Thr Ser Gln Glu Phe Val Glu
435 440 445

Lys Leu Thr Lys Arg Leu Lys Arg His Pro Glu Glu Thr Gly Gly Phe
450 455 460

Gln Glu Ala Pro Leu Ala Tyr Asp Ala Ile Trp Ala Leu Ala Leu Ala
465 470 475 480

Leu Asn Lys Thr Ser Gly Gly Gly Gly Arg Ser Gly Val Arg Leu Glu
485 490 495

Asp Phe Asn Tyr Asn Asn Gln Thr Ile Thr Asp Gln Ile Tyr Arg Ala
500 505 510

Met Asn Ser Ser Ser Phe Glu Gly Val Ser Gly His Val Val Phe Asp
515 520 525

```
Ala Ser Gly Ser Arg Met Ala Trp Thr Leu Ile Glu Gln Leu Gln Gly
    530                 535                 540

Gly Ser Tyr Lys Lys Ile Gly Tyr Tyr Asp Ser Thr Lys Asp Asp Leu
545                 550                 555                 560

Ser Trp Ser Lys Thr Asp Lys Trp Ile Gly Gly Ser Pro Pro Ala Asp
                565                 570                 575

Gln Thr Leu Val Ile Lys Thr Phe Arg Phe Leu Ser Gln Lys Leu Phe
            580                 585                 590

Ile Ser Val Ser Val Leu Ser Ser Leu Gly Ile Val Leu Ala Val Val
        595                 600                 605

Cys Leu Ser Phe Asn Ile Tyr Asn Ser His Val Arg Tyr Ile Gln Asn
    610                 615                 620

Ser Gln Pro Asn Leu Asn Asn Leu Thr Ala Val Gly Cys Ser Leu Ala
625                 630                 635                 640

Leu Ala Ala Val Phe Pro Leu Gly Leu Asp Gly Tyr His Ile Gly Arg
                645                 650                 655

Asn Gln Phe Pro Phe Val Cys Gln Ala Arg Leu Trp Leu Leu Gly Leu
            660                 665                 670

Gly Phe Ser Leu Gly Tyr Gly Ser Met Phe Thr Lys Ile Trp Trp Val
        675                 680                 685

His Thr Val Phe Thr Lys Lys Glu Glu Lys Lys Glu Trp Arg Lys Thr
    690                 695                 700

Leu Glu Pro Trp Lys Leu Tyr Ala Thr Val Gly Leu Leu Val Gly Met
705                 710                 715                 720

Asp Val Leu Thr Leu Ala Ile Trp Gln Ile Val Asp Pro Leu His Arg
                725                 730                 735

Thr Ile Glu Thr Phe Ala Lys Glu Glu Pro Lys Glu Asp Ile Asp Val
            740                 745                 750

Ser Ile Leu Pro Gln Leu Glu His Cys Ser Ser Arg Lys Met Asn Thr
        755                 760                 765

Trp Leu Gly Ile Phe Tyr Gly Tyr Lys Gly Leu Leu Leu Leu Leu Gly
    770                 775                 780

Ile Phe Leu Ala Tyr Glu Thr Lys Ser Val Ser Thr Glu Lys Ile Asn
785                 790                 795                 800

Asp His Arg Ala Val Gly Met Ala Ile Tyr Asn Val Ala Val Leu Cys
                805                 810                 815

Leu Ile Thr Ala Pro Val Thr Met Ile Leu Ser Ser Gln Gln Asp Ala
            820                 825                 830
```

Ala Phe Ala Phe Ala Ser Leu Ala Ile Val Phe Ser Ser Tyr Ile Thr
835 840 845

Leu Val Val Leu Phe Val Pro Lys Met Arg Arg Leu Ile Thr Arg Gly
850 855 860

Glu Trp Gln Ser Glu Ala Gln Asp Thr Met Lys Thr Gly Ser Ser Thr
865 870 875 880

Asn Asn Asn Glu Glu Glu Lys Ser Arg Leu Leu Glu Lys Glu Asn Arg
885 890 895

Glu Leu Glu Lys Ile Ile Ala Glu Lys Glu Glu Arg Val Ser Glu Leu
900 905 910

Arg His Gln Leu Gln Ser Arg Gln Gln Leu Arg Ser Arg Arg His Pro
915 920 925

Pro Thr Pro Pro Glu Pro Ser Gly Gly Leu Pro Arg Gly Pro Pro Glu
930 935 940

Pro Pro Asp Arg Leu Ser Cys Asp Gly Ser Arg Val His Leu Leu Tyr
945 950 955 960
Lys

<210> 8
<211> 844
<212> PRT
<213> Human

<400> 8

Met Gly Pro Gly Ala Pro Phe Ala Arg Val Gly Trp Pro Leu Pro Leu
1 5 10 15

Leu Val Val Met Ala Ala Gly Val Ala Pro Val Trp Ala Ser His Ser
20 25 30

Pro His Leu Pro Arg Pro His Ser Arg Val Pro Pro His Pro Ser Ser
35 40 45

Glu Arg Arg Ala Val Tyr Ile Gly Ala Leu Phe Pro Met Ser Gly Gly
50 55 60

Trp Pro Gly Gly Gln Ala Cys Gln Pro Ala Val Glu Met Ala Leu Glu
65 70 75 80

Asp Val Asn Ser Arg Arg Asp Ile Leu Pro Asp Tyr Glu Leu Lys Leu
85 90 95

Ile His His Asp Ser Lys Cys Asp Pro Gly Gln Ala Thr Lys Tyr Leu
100 105 110

Tyr Glu Leu Leu Tyr Asn Asp Pro Ile Lys Ile Ile Leu Met Pro Gly
115 120 125

```
Cys Ser Ser Val Ser Thr Leu Val Ala Glu Ala Ala Arg Met Trp Asn
    130                 135                 140

Leu Ile Val Leu Ser Tyr Gly Ser Ser Ser Pro Ala Leu Ser Asn Arg
145                 150                 155                 160

Gln Arg Phe Pro Thr Phe Phe Arg Thr His Pro Ser Ala Thr Leu His
                165                 170                 175

Asn Pro Thr Arg Val Lys Leu Phe Glu Lys Trp Gly Trp Lys Lys Ile
            180                 185                 190

Ala Thr Ile Gln Gln Thr Thr Glu Val Phe Thr Ser Thr Leu Asp Asp
        195                 200                 205

Leu Glu Glu Arg Val Lys Glu Ala Gly Ile Glu Ile Thr Phe Arg Gln
    210                 215                 220

Ser Phe Phe Ser Asp Pro Ala Val Pro Val Lys Asn Leu Lys Arg Gln
225                 230                 235                 240

Asp Ala Arg Ile Ile Val Gly Leu Phe Tyr Glu Thr Glu Ala Arg Lys
                245                 250                 255

Val Phe Cys Glu Val Tyr Lys Glu Arg Leu Phe Gly Lys Lys Tyr Val
            260                 265                 270

Trp Phe Leu Ile Gly Trp Tyr Ala Asp Asn Trp Phe Lys Ile Tyr Asp
        275                 280                 285

Pro Ser Ile Asn Cys Thr Val Asp Glu Met Thr Glu Ala Val Glu Gly
    290                 295                 300

His Ile Thr Thr Glu Ile Val Met Leu Asn Pro Ala Asn Thr Arg Ser
305                 310                 315                 320

Ile Ser Asn Met Thr Ser Gln Glu Phe Val Glu Lys Leu Thr Lys Arg
                325                 330                 335

Leu Lys Arg His Pro Glu Glu Thr Gly Gly Phe Gln Glu Ala Pro Leu
            340                 345                 350

Ala Tyr Asp Ala Ile Trp Ala Leu Ala Leu Ala Leu Asn Lys Thr Ser
        355                 360                 365

Gly Gly Gly Gly Arg Ser Gly Val Arg Leu Glu Asp Phe Asn Tyr Asn
    370                 375                 380

Asn Gln Thr Ile Thr Asp Gln Ile Tyr Arg Ala Met Asn Ser Ser Ser
385                 390                 395                 400

Phe Glu Gly Val Ser Gly His Val Val Phe Asp Ala Ser Gly Ser Arg
                405                 410                 415

Met Ala Trp Thr Leu Ile Glu Gln Leu Gln Gly Gly Ser Tyr Lys Lys
            420                 425                 430
```

Ile Gly Tyr Tyr Asp Ser Thr Lys Asp Asp Leu Ser Trp Ser Lys Thr
435 440 445

Asp Lys Trp Ile Gly Gly Ser Pro Pro Ala Asp Gln Thr Leu Val Ile
450 455 460

Lys Thr Phe Arg Phe Leu Ser Gln Lys Leu Phe Ile Ser Val Ser Val
465 470 475 480

Leu Ser Ser Leu Gly Ile Val Leu Ala Val Val Cys Leu Ser Phe Asn
485 490 495

Ile Tyr Asn Ser His Val Arg Tyr Ile Gln Asn Ser Gln Pro Asn Leu
500 505 510

Asn Asn Leu Thr Ala Val Gly Cys Ser Leu Ala Leu Ala Ala Val Phe
515 520 525

Pro Leu Gly Leu Asp Gly Tyr His Ile Gly Arg Asn Gln Phe Pro Phe
530 535 540

Val Cys Gln Ala Arg Leu Trp Leu Leu Gly Leu Gly Phe Ser Leu Gly
545 550 555 560

Tyr Gly Ser Met Phe Thr Lys Ile Trp Trp Val His Thr Val Phe Thr
565 570 575

Lys Lys Glu Glu Lys Lys Glu Trp Arg Lys Thr Leu Glu Pro Trp Lys
580 585 590

Leu Tyr Ala Thr Val Gly Leu Leu Val Gly Met Asp Val Leu Thr Leu
595 600 605

Ala Ile Trp Gln Ile Val Asp Pro Leu His Arg Thr Ile Glu Thr Phe
610 615 620

Ala Lys Glu Glu Pro Lys Glu Asp Ile Asp Val Ser Ile Leu Pro Gln
625 630 635 640

Leu Glu His Cys Ser Ser Arg Lys Met Asn Thr Trp Leu Gly Ile Phe
645 650 655

Tyr Gly Tyr Lys Gly Leu Leu Leu Leu Leu Gly Ile Phe Leu Ala Tyr
660 665 670

Glu Thr Lys Ser Val Ser Thr Glu Lys Ile Asn Asp His Arg Ala Val
675 680 685

Gly Met Ala Ile Tyr Asn Val Ala Val Leu Cys Leu Ile Thr Ala Pro
690 695 700

Val Thr Met Ile Leu Ser Ser Gln Gln Asp Ala Ala Phe Ala Phe Ala
705 710 715 720

Ser Leu Ala Ile Val Phe Ser Ser Tyr Ile Thr Leu Val Val Leu Phe
725 730 735

```
Val Pro Lys Met Arg Arg Leu Ile Thr Arg Gly Glu Trp Gln Ser Glu
            740                 745                 750

Ala Gln Asp Thr Met Lys Thr Gly Ser Ser Thr Asn Asn Asn Glu Glu
        755                 760                 765

Glu Lys Ser Arg Leu Leu Glu Lys Glu Asn Arg Glu Leu Glu Lys Ile
    770                 775                 780

Ile Ala Glu Lys Glu Glu Arg Val Ser Glu Leu Arg His Gln Leu Gln
785                 790                 795                 800

Ser Arg Gln Gln Leu Arg Ser Arg Arg His Pro Pro Thr Pro Pro Glu
                805                 810                 815

Pro Ser Gly Gly Leu Pro Arg Gly Pro Pro Glu Pro Pro Asp Arg Leu
            820                 825                 830

Ser Cys Asp Gly Ser Arg Val His Leu Leu Tyr Lys
        835                 840
```

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<210> 9
<211> 3554
<212> DNA
<213> Human

<220>
<221> CDS
<222> (1)...(3234)

<400> 9
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atg gca ttt tat agc tgc tgc tgg gtc ctc ttg gca ctc acc tgg cac      48
Met Ala Phe Tyr Ser Cys Cys Trp Val Leu Leu Ala Leu Thr Trp His
 1               5                  10                  15

acc tct gcc tac ggg cca gac cag cga gcc caa aag aag ggg gac att      96
Thr Ser Ala Tyr Gly Pro Asp Gln Arg Ala Gln Lys Lys Gly Asp Ile
            20                  25                  30

atc ctt ggg ggg ctc ttt cct att cat ttt gga gta gca gct aaa gat     144
Ile Leu Gly Gly Leu Phe Pro Ile His Phe Gly Val Ala Ala Lys Asp
        35                  40                  45

caa gat ctc aaa tca agg ccg gag tct gtg gaa tgt atc agg tat aat     192
Gln Asp Leu Lys Ser Arg Pro Glu Ser Val Glu Cys Ile Arg Tyr Asn
    50                  55                  60

ttc cgt ggg ttt cgc tgg tta cag gct atg ata ttt gcc ata gag gag     240
Phe Arg Gly Phe Arg Trp Leu Gln Ala Met Ile Phe Ala Ile Glu Glu
 65                  70                  75                  80

ata aac agc agc cca gcc ctt ctt ccc aac ttg acg ctg gga tac agg     288
Ile Asn Ser Ser Pro Ala Leu Leu Pro Asn Leu Thr Leu Gly Tyr Arg
                85                  90                  95
```

```
ata ttt gac act tgc aac acc gtt tct aag gcc ttg gaa gcc acc ctg      336
Ile Phe Asp Thr Cys Asn Thr Val Ser Lys Ala Leu Glu Ala Thr Leu
            100                 105                 110

agt ttt gtt gct caa aac aaa att gat tct ttg aac ctt gat gag ttc      384
Ser Phe Val Ala Gln Asn Lys Ile Asp Ser Leu Asn Leu Asp Glu Phe
        115                 120                 125

tgc aac tgc tca gag cac att ccc tct acg att gct gtg gtg gga gca      432
Cys Asn Cys Ser Glu His Ile Pro Ser Thr Ile Ala Val Val Gly Ala
    130                 135                 140

act ggc tca ggc gtc tcc acg gca gtg gca aat ctg ctg ggg ctc ttc      480
Thr Gly Ser Gly Val Ser Thr Ala Val Ala Asn Leu Leu Gly Leu Phe
145                 150                 155                 160

tac att ccc cag gtc agt tat gcc tcc tcc agc aga ctc ctc agc aac      528
Tyr Ile Pro Gln Val Ser Tyr Ala Ser Ser Ser Arg Leu Leu Ser Asn
                165                 170                 175

aag aat caa ttc aag tct ttc ctc cga acc atc ccc aat gat gag cac      576
Lys Asn Gln Phe Lys Ser Phe Leu Arg Thr Ile Pro Asn Asp Glu His
            180                 185                 190

cag gcc act gcc atg gca gac atc atc gag tat ttc cgc tgg aac tgg      624
Gln Ala Thr Ala Met Ala Asp Ile Ile Glu Tyr Phe Arg Trp Asn Trp
        195                 200                 205

gtg ggc aca att gca gct gat gac gac tat ggg cgg ccg ggg att gag      672
Val Gly Thr Ile Ala Ala Asp Asp Asp Tyr Gly Arg Pro Gly Ile Glu
    210                 215                 220

aaa ttc cga gag gaa gct gag gaa agg gat atc tgc atc gac ttc agt      720
Lys Phe Arg Glu Glu Ala Glu Glu Arg Asp Ile Cys Ile Asp Phe Ser
225                 230                 235                 240

gaa ctc atc tcc cag tac tct gat gag gaa gag atc cag cat gtg gta      768
Glu Leu Ile Ser Gln Tyr Ser Asp Glu Glu Glu Ile Gln His Val Val
                245                 250                 255

gag gtg att caa aat tcc acg gcc aaa gtc atc gtg gtt ttc tcc agt      816
Glu Val Ile Gln Asn Ser Thr Ala Lys Val Ile Val Val Phe Ser Ser
            260                 265                 270

ggc cca gat ctt gag ccc ctc atc aag gag att gtc cgg cgc aat atc      864
Gly Pro Asp Leu Glu Pro Leu Ile Lys Glu Ile Val Arg Arg Asn Ile
        275                 280                 285

acg ggc aag atc tgg ctg gcc agc gag gcc tgg gcc agc tcc tcc ctg      912
Thr Gly Lys Ile Trp Leu Ala Ser Glu Ala Trp Ala Ser Ser Ser Leu
    290                 295                 300

atc gcc atg cct cag tac ttc cac gtg gtt ggc ggc acc att gga ttc      960
Ile Ala Met Pro Gln Tyr Phe His Val Val Gly Gly Thr Ile Gly Phe
305                 310                 315                 320
```

gct ctg aag gct ggg cag atc cca ggc ttc cgg gaa ttc ctg aag aag 1008
Ala Leu Lys Ala Gly Gln Ile Pro Gly Phe Arg Glu Phe Leu Lys Lys
325 330 335

gtc cat ccc agg aag tct gtc cac aat ggt ttt gcc aag gag ttt tgg 1056
Val His Pro Arg Lys Ser Val His Asn Gly Phe Ala Lys Glu Phe Trp
340 345 350

gaa gaa aca ttt aac tgc cac ctc caa gaa ggt gca aaa gga cct tta 1104
Glu Glu Thr Phe Asn Cys His Leu Gln Glu Gly Ala Lys Gly Pro Leu
355 360 365

cct gtg gac acc ttt ctg aga ggt cac gaa gaa agt ggc gac agg ttt 1152
Pro Val Asp Thr Phe Leu Arg Gly His Glu Glu Ser Gly Asp Arg Phe
370 375 380

agc aac agc tcg aca gcc ttc cga ccc ctc tgt aca ggg gat gag aac 1200
Ser Asn Ser Ser Thr Ala Phe Arg Pro Leu Cys Thr Gly Asp Glu Asn
385 390 395 400

atc agc agt gtc gag acc cct tac ata gat tac acg cat tta cgg ata 1248
Ile Ser Ser Val Glu Thr Pro Tyr Ile Asp Tyr Thr His Leu Arg Ile
405 410 415

tcc tac aat gtg tac tta gca gtc tac tcc att gcc cac gcc ttg caa 1296
Ser Tyr Asn Val Tyr Leu Ala Val Tyr Ser Ile Ala His Ala Leu Gln
420 425 430

gat ata tat acc tgc tta cct ggg aga ggg ctc ttc acc aat ggc tcc 1344
Asp Ile Tyr Thr Cys Leu Pro Gly Arg Gly Leu Phe Thr Asn Gly Ser
435 440 445

tgt gca gac atc aag aaa gtt gag gcg tgg cag gtc ctg aag cac cta 1392
Cys Ala Asp Ile Lys Lys Val Glu Ala Trp Gln Val Leu Lys His Leu
450 455 460

cgg cat cta aac ttt aca aac aat atg ggg gag cag gtg acc ttt gat 1440
Arg His Leu Asn Phe Thr Asn Asn Met Gly Glu Gln Val Thr Phe Asp
465 470 475 480

gag tgt ggt gac ctg gtg ggg aac tat tcc atc atc aac tgg cac ctc 1488
Glu Cys Gly Asp Leu Val Gly Asn Tyr Ser Ile Ile Asn Trp His Leu
485 490 495

tcc cca gag gat ggc tcc atc gtg ttt aag gaa gtc ggg tat tac aac 1536
Ser Pro Glu Asp Gly Ser Ile Val Phe Lys Glu Val Gly Tyr Tyr Asn
500 505 510

gtc tat gcc aag aag gga gaa aga ctc ttc atc aac gag gag aaa atc 1584
Val Tyr Ala Lys Lys Gly Glu Arg Leu Phe Ile Asn Glu Glu Lys Ile
515 520 525

ctg tgg agt ggg ttc tcc agg gag gtg ccc ttc tcc aac tgc agc cga 1632
Leu Trp Ser Gly Phe Ser Arg Glu Val Pro Phe Ser Asn Cys Ser Arg
530 535 540

gac tgc ctg gca ggg acc agg aaa ggg atc att gag ggg gag ccc acc 1680
Asp Cys Leu Ala Gly Thr Arg Lys Gly Ile Ile Glu Gly Glu Pro Thr
545 550 555 560

tgc tgc ttt gag tgt gtg gag tgt cct gat ggg gag tat agt gat gag 1728
Cys Cys Phe Glu Cys Val Glu Cys Pro Asp Gly Glu Tyr Ser Asp Glu
565 570 575

aca gat gcc agt gcc tgt aac aag tgc cca gat gac ttc tgg tcc aat 1776
Thr Asp Ala Ser Ala Cys Asn Lys Cys Pro Asp Asp Phe Trp Ser Asn
580 585 590

gag aac cac acc tcc tgc att gcc aag gag atc gag ttt ctg tcg tgg 1824
Glu Asn His Thr Ser Cys Ile Ala Lys Glu Ile Glu Phe Leu Ser Trp
595 600 605

acg gag ccc ttt ggg atc gca ctc acc ctc ttt gcc gtg ctg ggc att 1872
Thr Glu Pro Phe Gly Ile Ala Leu Thr Leu Phe Ala Val Leu Gly Ile
610 615 620

ttc ctg aca gcc ttt gtg ctg ggt gtg ttt atc aag ttc cgc aac aca 1920
Phe Leu Thr Ala Phe Val Leu Gly Val Phe Ile Lys Phe Arg Asn Thr
625 630 635 640

ccc att gtc aag gcc acc aac cga gag ctc tcc tac ctc ctc ctc ttc 1968
Pro Ile Val Lys Ala Thr Asn Arg Glu Leu Ser Tyr Leu Leu Leu Phe
645 650 655

tcc ctg ctc tgc tgc ttc tcc agc tcc ctg ttc ttc atc ggg gag ccc 2016
Ser Leu Leu Cys Cys Phe Ser Ser Ser Leu Phe Phe Ile Gly Glu Pro
660 665 670

cag gac tgg acg tgc cgc ctg cgc cag ccg gcc ttt ggc atc agc ttc 2064
Gln Asp Trp Thr Cys Arg Leu Arg Gln Pro Ala Phe Gly Ile Ser Phe
675 680 685

gtg ctc tgc atc tca tgc atc ctg gtg aaa acc aac cgt gtc ctc ctg 2112
Val Leu Cys Ile Ser Cys Ile Leu Val Lys Thr Asn Arg Val Leu Leu
690 695 700

gtg ttt gag gcc aag atc ccc acc agc ttc cac cgc aag tgg tgg ggg 2160
Val Phe Glu Ala Lys Ile Pro Thr Ser Phe His Arg Lys Trp Trp Gly
705 710 715 720

ctc aac ctg cag ttc ctg ctg gtt ttc ctc tgc acc ttc atg cag att 2208
Leu Asn Leu Gln Phe Leu Leu Val Phe Leu Cys Thr Phe Met Gln Ile
725 730 735

gtc atc tgt gtg atc tgg ctc tac acc gcg ccc ccc tca agc tac cgc 2256
Val Ile Cys Val Ile Trp Leu Tyr Thr Ala Pro Pro Ser Ser Tyr Arg
740 745 750

aac cag gag ctg gag gat gag atc atc ttc atc acg tgc cac gag ggc 2304
Asn Gln Glu Leu Glu Asp Glu Ile Ile Phe Ile Thr Cys His Glu Gly
755 760 765

tcc ctc atg gcc ctg ggc ttc ctg atc ggc tac acc tgc ctg ctg gct 2352
Ser Leu Met Ala Leu Gly Phe Leu Ile Gly Tyr Thr Cys Leu Leu Ala
770 775 780

gcc atc tgc ttc ttc ttt gcc ttc aag tcc cgg aag ctg ccg gag aac 2400
Ala Ile Cys Phe Phe Phe Ala Phe Lys Ser Arg Lys Leu Pro Glu Asn
785 790 795 800

ttc aat gaa gcc aag ttc atc acc ttc agc atg ctc atc ttc ttc atc 2448
Phe Asn Glu Ala Lys Phe Ile Thr Phe Ser Met Leu Ile Phe Phe Ile
805 810 815

gtc tgg atc tcc ttc att cca gcc tat gcc agc acc tat ggc aag ttt 2496
Val Trp Ile Ser Phe Ile Pro Ala Tyr Ala Ser Thr Tyr Gly Lys Phe
820 825 830

gtc tct gcc gta gag gtg att gcc atc ctg gca gcc agc ttt ggc ttg 2544
Val Ser Ala Val Glu Val Ile Ala Ile Leu Ala Ala Ser Phe Gly Leu
835 840 845

ctg gcg tgc atc ttc ttc aac aag atc tac atc att ctc ttc aag cca 2592
Leu Ala Cys Ile Phe Phe Asn Lys Ile Tyr Ile Ile Leu Phe Lys Pro
850 855 860

tcc cgc aac acc atc gag gag gtg cgt tgc agc acc gca gct cac gct 2640
Ser Arg Asn Thr Ile Glu Glu Val Arg Cys Ser Thr Ala Ala His Ala
865 870 875 880

ttc aag gtg gct gcc cgg gcc acg ctg cgc cgc agc aac gtc tcc cgc 2688
Phe Lys Val Ala Ala Arg Ala Thr Leu Arg Arg Ser Asn Val Ser Arg
885 890 895

aag cgg tcc agc agc ctt gga ggc tcc acg gga tcc acc ccc tcc tcc 2736
Lys Arg Ser Ser Ser Leu Gly Gly Ser Thr Gly Ser Thr Pro Ser Ser
900 905 910

tcc atc agc agc aag agc aac agc gaa gac cca ttc cca cag ccc gag 2784
Ser Ile Ser Ser Lys Ser Asn Ser Glu Asp Pro Phe Pro Gln Pro Glu
915 920 925

agg cag aag cag cag cag ccg ctg gcc cta acc cag caa gag cag cag 2832
Arg Gln Lys Gln Gln Gln Pro Leu Ala Leu Thr Gln Gln Glu Gln Gln
930 935 940

cag cag ccc ctg acc ctc cca cag cag caa cga tct cag cag cag ccc 2880
Gln Gln Pro Leu Thr Leu Pro Gln Gln Gln Arg Ser Gln Gln Gln Pro
945 950 955 960

aga tgc aag cag aag gtc atc ttt ggc agc ggc acg gtc acc ttc tca 2928
Arg Cys Lys Gln Lys Val Ile Phe Gly Ser Gly Thr Val Thr Phe Ser
965 970 975

ctg agc ttt gat gag cct cag aag aac gcc atg gcc cac ggg aat tct 2976
Leu Ser Phe Asp Glu Pro Gln Lys Asn Ala Met Ala His Gly Asn Ser
980 985 990

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acg cac cag aac tcc ctg gag gcc cag aaa agc agc gat acg ctg acc     3024
Thr His Gln Asn Ser Leu Glu Ala Gln Lys Ser Ser Asp Thr Leu Thr
        995                 1000                1005

cga cac cag cca tta ctc ccg ctg cag tgc ggg gaa acg gac tta gat     3072
Arg His Gln Pro Leu Leu Pro Leu Gln Cys Gly Glu Thr Asp Leu Asp
    1010                1015                1020

ctg acc gtc cag gaa aca ggt ctg caa gga cct gtg ggt gga gac cag     3120
Leu Thr Val Gln Glu Thr Gly Leu Gln Gly Pro Val Gly Gly Asp Gln
1025                1030                1035                1040

cgg cca gag gtg gag gac cct gaa gag ttg tcc cca gca ctt gta gtg     3168
Arg Pro Glu Val Glu Asp Pro Glu Glu Leu Ser Pro Ala Leu Val Val
                1045                1050                1055

tcc agt tca cag agc ttt gtc atc agt ggt gga ggc agc act gtt aca     3216
Ser Ser Ser Gln Ser Phe Val Ile Ser Gly Gly Gly Ser Thr Val Thr
            1060                1065                1070

gaa aac gta gtg aat tca                                             3234
Glu Asn Val Val Asn Ser
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/07352

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K14/47 C07K14/705 C12N15/12 C07K16/28 C12N5/06
A01K67/027

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 46675 A (NOVARTIS AG) 11 December 1997 (1997-12-11) cited in the application abstract page 6, paragraph 2 -page 7, paragraph 1 page 16, paragraph 2 -page 21, paragraph 2; examples 1-10 ---	1-33
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
23 September 1999	08/10/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Mateo Rosell, A.M.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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E	WO 99 20751 A (BOROWSKY BETH ;JONES KENNETH A (US); LAZ THOMAS M (US); SYNAPTIC P) 29 April 1999 (1999-04-29) fig 1a-e abstract page 6-19 page 91, line 1 -page 123, line 6	1-24, 26-33
E	EP 0 937 777 A (SMITHKLINE BEECHAM PLC ;SMITHKLINE BEECHAM CORP (US)) 25 August 1999 (1999-08-25) see SEQ.ID.N.1 and 3. abstract page 3, line 10-25 page 6, line 44 -page 11, line 11	1-24, 26-32

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/07352

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